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THE ANNALS OF THORACIC SURGERY

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A recent nationwide analysis revealed that each postoperative wound infection represents a nonreimbursable loss to a hospital of $2,467, on average.[2] By reducing the rate of infection, ZINACEF can help reduce these losses.

1. Slama TG, Sklar SJ, Misinski J, et al: Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. *Antimicrob Agents Chemother* 1986;29:744-747.
2. Haley RW, White JW, Culver DH, et al: The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. *JAMA* 1987;257:1611-1614.

Please consult Brief Summary of Prescribing Information on next page before prescribing or administering ZINACEF.

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ZIN 346

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Brief summary. Before prescribing, consult complete Prescribing Information.

INDICATIONS AND USAGE: ZINACEF® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *S pneumoniae* (formerly *D pneumoniae), H influenzae* (including ampicillin-resistant strains), *Klebsiella* sp, *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, and *E coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* sp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes, E coli, Klebsiella* sp, and *Enterobacter* sp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae, E coli, H influenzae* (including ampicillin-resistant strains), and *Klebsiella* sp.
5. **Meningitis** caused by *S pneumoniae, H influenzae* (including ampicillin-resistant strains), *N meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *N gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. ZINACEF has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to ZINACEF.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, ZINACEF may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF® (sterile cefuroxime sodium, Glaxo) should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of ZINACEF has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that ZINACEF therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: ZINACEF® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although ZINACEF® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving ZINACEF.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since ZINACEF is excreted in human milk, caution should be exercised when ZINACEF is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: ZINACEF® is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence was seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

HOW SUPPLIED ZINACEF® is a dry, white to off-white powder supplied in vials and infusion packs.

Each vial contains cefuroxime sodium equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime. ZINACEF in the dry state should be stored between 15° to 30°C (59° to 86°F), and protected from light.

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October 1987
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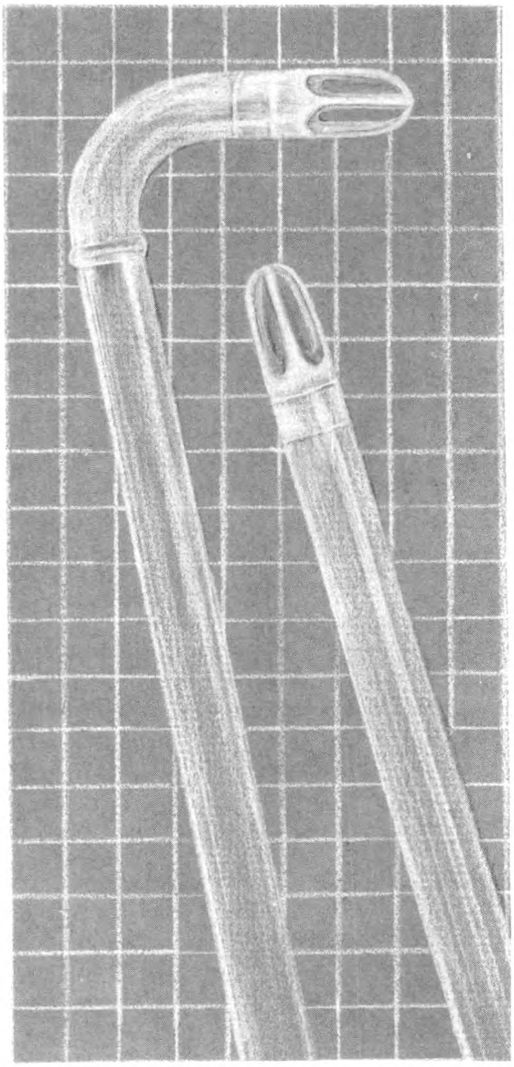

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Volume 49 Number 1

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January 1990

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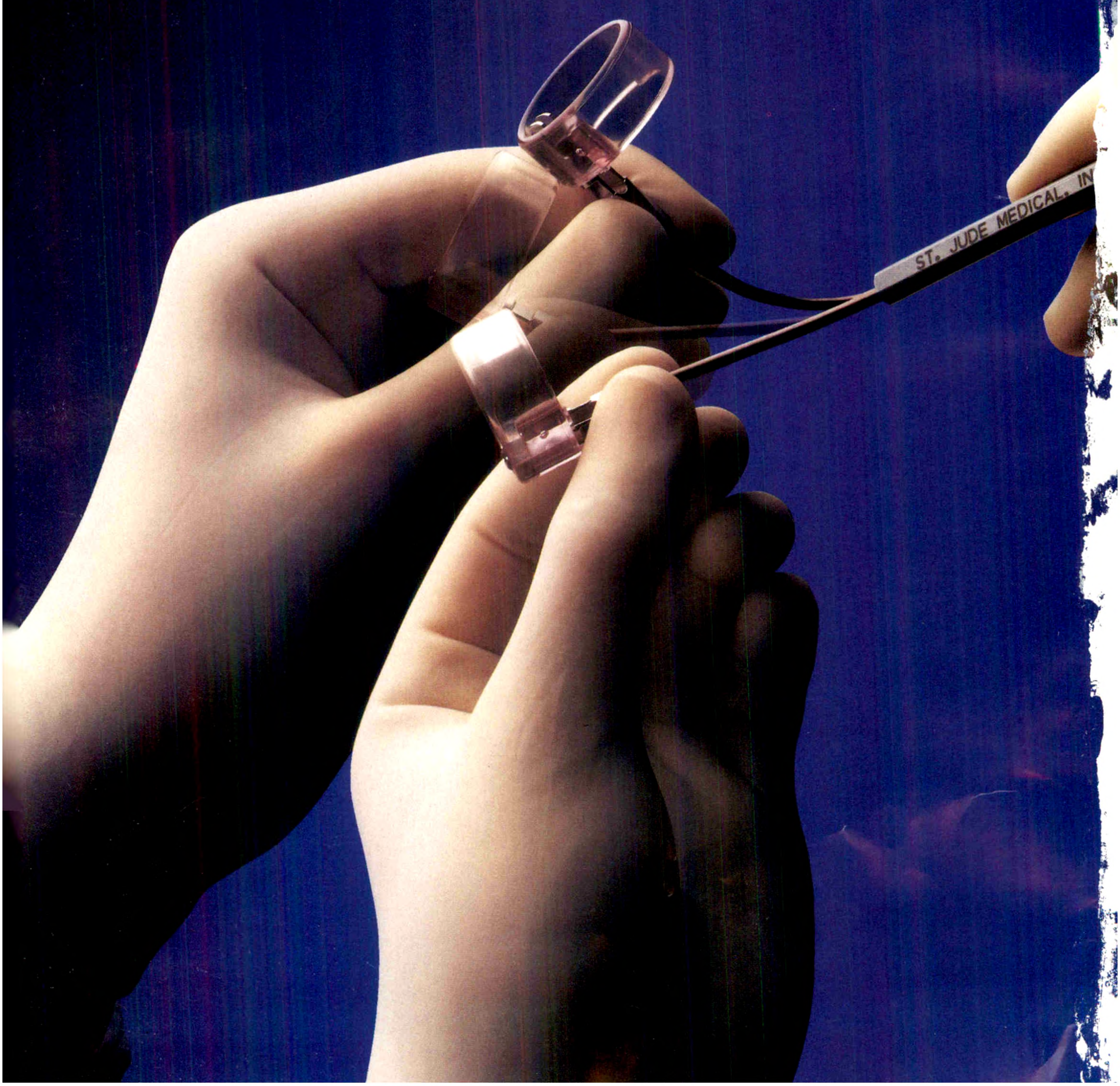

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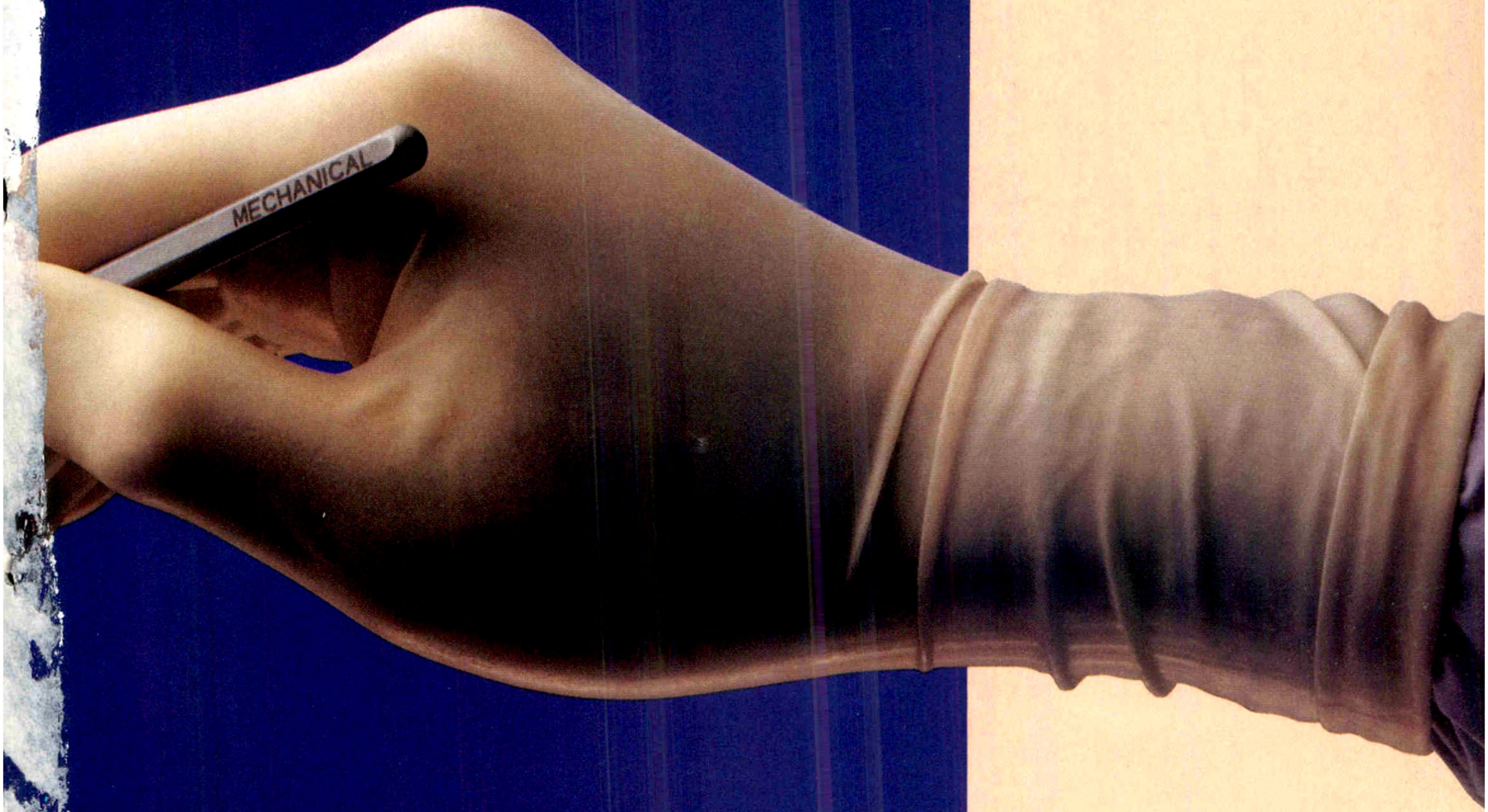

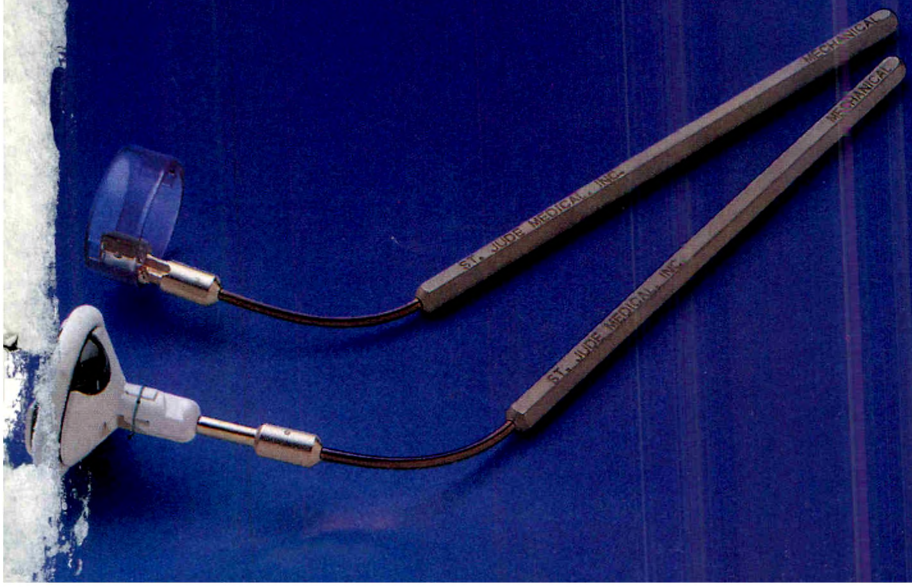

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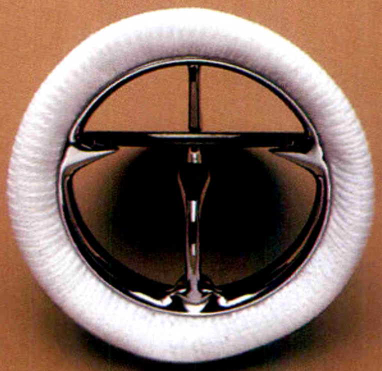

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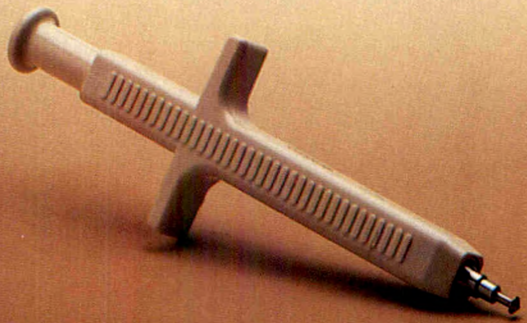

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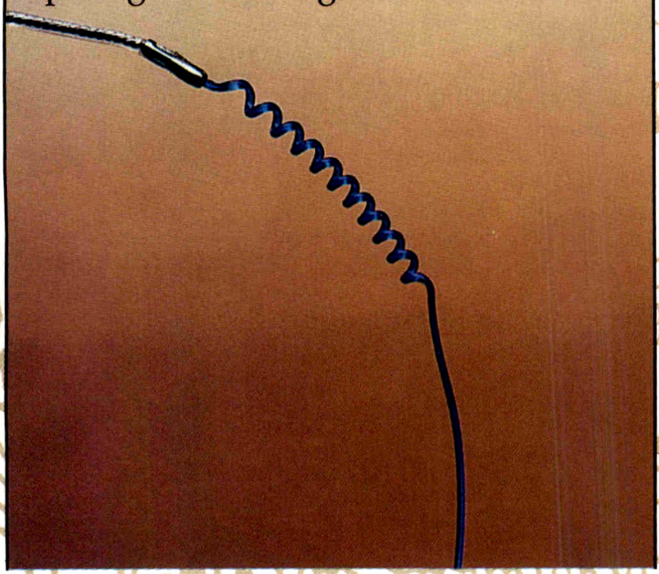

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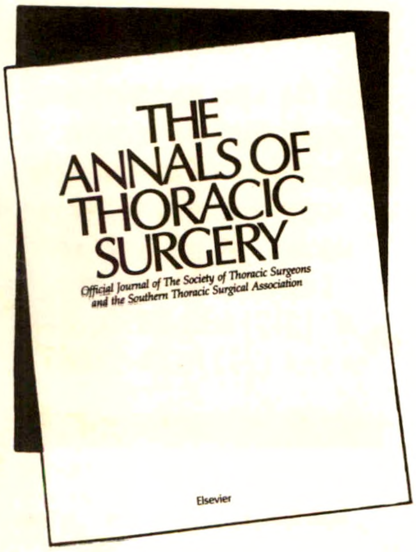
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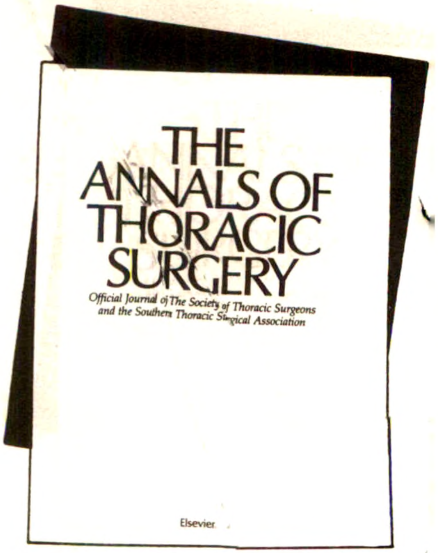
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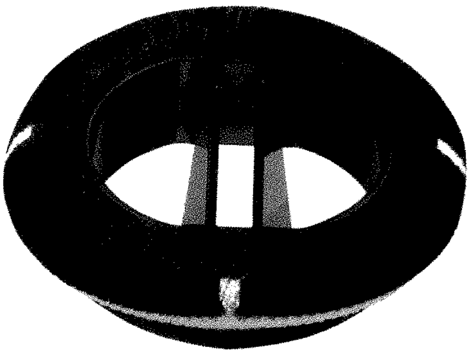

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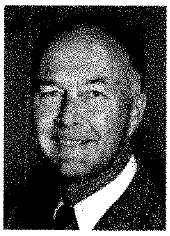
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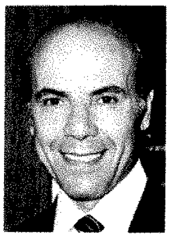
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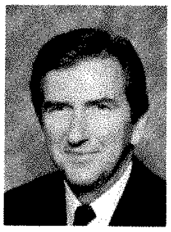
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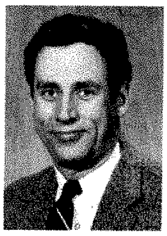
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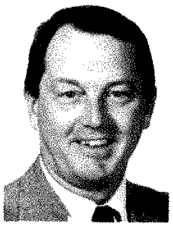
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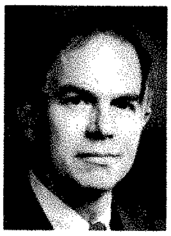
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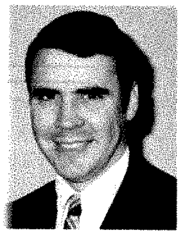
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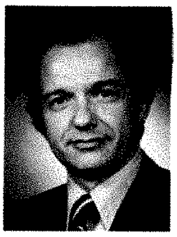
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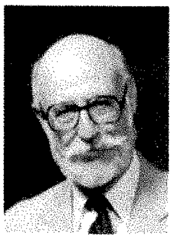
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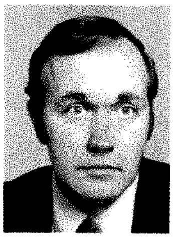
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Welcoming Remarks

James I. Hudson, MD

Associate Dean for Academic Administration, University of Maryland School of Medicine, Baltimore, Maryland

For me it is a pleasant experience—one associated with a feeling of honor and some history—to greet you on behalf of the University of Maryland School of Medicine. All of us from Baltimore are extremely pleased that you have chosen our city as the site of your Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons and the Twenty-third Postgraduate Program of The Society. It goes without saying that we are quite proud of the contributions made by the two major medical institutions in Baltimore to the field of thoracic and cardiovascular surgery throughout this century.

For someone as old as I, 25 years seems a relatively short time—a blink of the eye—in the continuum of scientific advancement, but when one looks back to the year of the organization of The Society, 1964, that year does seem a bit remote. In anticipation of this meeting I wandered recently through our Health Sciences Library and searched through one of the more prominent journals in the field at the time: *The Journal of Thoracic and Cardiovascular Surgery*. Scanning the September 1964 issue, 25 years ago to the date, I noted the following contributed articles: a report on early results of clinical homograft valve transplantation, another early report on sutureless aortic and mitral prosthetic valves, a report on the results of a number of cases of bilateral pulmonary resection for tuberculosis, and a paper on the experimental evaluation of epicardectomy and Ivalon sponge operation for the treatment of coronary artery disease. Perhaps that recitation more than any other thing that I could mention in this brief greeting serves to point up just how far you have come.

We live in a different world now than existed in those rather innocent, naive, and exuberant years of the early 1960s when everything appeared within our reach and within our capacity to achieve, when our resources seemed boundless, and it seemed that we had only to exercise our scientific imagination to bring all services to all persons in need of them. Over the 2½ decades, we have learned that we must contend with the reality of limited resources. Ultimately, the question of rationing—or at least prioritization—in the use of medical and surgical interventions looms around the corner. Already, we live in a era of public and payor accountability; an era in which, quite rightly I believe, we are witnessing an increased emphasis on carefully constructed and statistically sound outcome studies. These investigations should provide us, better than any time before, with more precise information on not only costs but benefits in terms of effectiveness consistent with patient values and expectancies. This information is critically important to the clinical decisions we must make on a day-to-day basis.

In this vein, I concluded a cursory review of the 56 papers scheduled for your scientific sessions in this conference and found, not unexpectedly, that approximately 40% will address either detailed outcome studies, preoperative risk assessment, or precise indications for various surgical interventions.

Ladies and Gentlemen, all of us here who labor at the interface of academic, clinical, and investigative medicine stand in the midst of continued vast opportunities to contribute to the public good, while at the same time we have clearly entered an era coined by Arnold Relman as one of "assessment and accountability." The papers you will hear during this session, especially your Twenty-fifth Anniversary Address on advances in general thoracic surgery by David Skinner and the address on cardiac surgery by John Kirklin will undoubtedly underscore this.

On behalf of the University I extend you best wishes for an informative and elevating three-day experience. Thank you.

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

Address reprint requests to Dr Hudson, The University of Maryland School of Medicine, 655 W Baltimore St, Baltimore, MD 21201.

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Welcoming Remarks

Richard S. Ross, MD

Dean of the Medical Faculty, Johns Hopkins University School of Medicine, Baltimore, Maryland

It is my great pleasure to welcome you to Baltimore during the centennial year of the Johns Hopkins Medical Institutions. On the seventh of May, 1889, the doors of the Johns Hopkins Hospital opened for the first time and, a few years later, in 1893 the medical school opened. We began the celebration of the centennial year in May and June of this year, and it will continue for 12 months, concluding in June of 1990. Many national societies will be meeting here during this, the centennial year. You, by choosing Baltimore as the site of your 1989 meeting, are contributing to our celebration.

As we prepared for the centennial, we refreshed our memory about Hopkins history. You will be interested in a few stories about our beginnings. The first concerns the very origins of the medical school, which almost didn't come into being.

Mr Johns Hopkins, a Quaker merchant of Baltimore, left $7 million in his will and directed the Trustees to form a hospital and a university; he indicated his intention that there would be in the university a medical school that would make use of the hospital for its teaching. When the time came to build the medical school, the country was in a depression and there was no money for a medical school. Therefore, it was decided to cancel plans for the medical school.

At that point, a group of young women of Baltimore, many of whom were daughters of Trustees, raised money to make it possible for the medical school to be formed. They offered the money to the Trustees with the condition that if they accepted the money, they would have to agree to accept women into the School of Medicine and accord them all the rights and privileges accorded to male medical students. The Trustees turned down this offer. The women then increased the amount of money, and eventually, the prudent Trustees took the money and took the women; indeed, there have been women in the School of Medicine since the very first class.

We have celebrated this bit of history and many others in this centennial year, which began in May. Another point of particular interest to surgeons would be the story about the beginning of rubber gloves at Johns Hopkins. William Stewart Halsted's scrub nurse had a problem with dermatitis on her hands from handwashing and strong antiseptics. To protect this young woman's hands, Halsted asked the Goodyear Rubber Company to make a pair of rubber gloves. This was done; her hands were cured, and eventually Halsted married the scrub nurse.

There are many other wonderful stories of those early days, and many of the recent past, especially of the 1940s when Alfred Blalock and Helen Taussig developed the technique of subclavian pulmonary anastomosis for the treatment of patients with tetralogy of Fallot. The remarkable role of Dr Blalock's technician, Vivien Thomas, in the perfection of the surgical technique has also become recognized. Although no longer the operation of choice for the tetralogy, this operation is recognized for its role in opening the era of cardiac surgery and providing a stimulus to the sister specialty of cardiology. I note with interest that contributions from Hopkins to the treatment of this disease continue as evidenced by the second paper on this program, which deals with total correction of the tetralogy of Fallot.

This is a historic place for surgeons and all others in medicine. You are adding to the luster of our celebration by choosing Baltimore as the site of your 1989 meeting.

Welcome and best wishes for a successful conference.

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

Address reprint requests to Dr Ross, The Johns Hopkins School of Medicine, 720 Rutland Ave, Baltimore, MD 21205.

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Welcoming Remarks

The Honorable Kurt Schmoke
Mayor, Baltimore, Maryland

Good morning, ladies and gentlemen. I am extremely pleased and honored to welcome this distinguished delegation of The Society of Thoracic Surgeons to Baltimore, and on behalf of all the citizens of our city, I want to wish you a highly successful and pleasurable Twenty-fifth Anniversary Meeting.

We are glad that The Society of Thoracic Surgeons chose Baltimore as the site for this important event. In coming to Baltimore, you are in a sense returning to your own roots. As many of you know, it was a Baltimore surgeon, Dr Adams Cowley, who, along with many others, led the movement in the early 1960s to establish this venerable organization.

As leaders in the field of heart and lung disease, members of this Society have helped generations of people to live longer, healthier, and more productive lives. All of us in Baltimore and around the country are deeply appreciative of the research and educational programs that you have sponsored over the last 25 years. Your dedication and hard work have saved lives and brought us closer to finding remedies to major public health problems.

It is certainly appropriate also, as has been mentioned, that you have come to Baltimore during the Johns Hopkins Centennial celebrations. We are very proud of the extraordinary accomplishments of Johns Hopkins, The University of Maryland School of Medicine, and other leading scientific organizations that have made their home in Baltimore.

We are also very proud of our local surgeons, many of whom are present here today. Their expertise and creativity have helped establish Baltimore as an international center of medical and scientific research.

I hope that all of you in the next few days get an opportunity to visit these fine medical institutions. I do not want you to think, however, that just because we are the home to leading medical schools and facilities we are in any way resting on our laurels. The University of Maryland will be undergoing major expansion over the next few years. Johns Hopkins is about to begin building a major new facility for medical research, and we also hope to continue Baltimore's reputation as a leader in international research by building what we call the Christopher Columbus Center of Marine Research and Exploration down at the Inner Harbor. The Center's research is expected to lead to, among other things, the development of new lifesaving medicines.

As mayor, I want to make sure that Baltimore's continuing growth as a scientific center, as well as its continually growing economy, will benefit our most valuable assets, which, of course, are the citizens of this city. That is why I have made public education and literacy top priorities for this community. I want to broaden the educational and career opportunities for all of our citizens, and we have set as our goal to make Baltimore known as The City That Reads.

So, again, I want to welcome all of you to Baltimore. I know that this conference will be very successful and that you will enjoy your stay here, and I hope that you will return soon.

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

Address reprint requests to Mr Schmoke, 100 N Holiday St, 250 City Hall, Baltimore, MD 21202.

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Philosophy 1

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Members of The Society of Thoracic Surgeons, friends, and guests: I want to thank all the members of The Society of Thoracic Surgeons for allowing me to serve as your president. I have been a member of The Society since its inception 25 years ago, when I was only 2 years out of my training program. Being selected as your president is beyond doubt the highest honor ever accorded me by my colleagues, and for this I thank you most sincerely.

On such an occasion, it is certainly customary and very appropriate that one identifies and recognizes those individuals who stimulated, directed, and fashioned one's career.

When I returned from military service to complete my surgical training, I became acquainted with Dr Hiram Langston (Fig 1). It was Dr Langston who prompted and encouraged me to continue my surgical training into the field of thoracic surgery. It was under his tutelage and that of his associate, Dr Noble Correll, that I first learned the disciplines and technical skills necessary in our specialty. Dr Langston was (and is) a superb teacher, adviser, and confidante, but perhaps most of all, he is an excellent role model whose conduct of his personal and professional career we could all well emulate. I thank Dr Langston for his early and continuing friendship.

My first exposure to cardiac surgery came under the direction of Drs John C. Jones and Bert W. Meyer (Fig 2). These two men exposed me to and stimulated my interest in surgery on the heart and great vessels. Bert, in particular, through his teaching and assisting, both in the operating room and in the research laboratory, directed the development of what skills I have in the field of heart surgery. After the completion of my training, I became associated with these two men and subsequently they became my partners. For their encouragement, help, trust, and friendship I would like to recognize these two fine men—indeed, pioneers in our specialty.

Additionally, I would like to recognize my partners, whose friendship, advice, and help make my professional career most fulfilling. They are Quentin Stiles, Bernard Tucker, Richard Hughes, Richard Hurvitz, Winfield Wells, and John Goodwin. It is through the mutual efforts of these skillful surgeons, teachers, and caring physicians that I have achieved the honor of serving as your president, and I most gratefully share this honor with them.

At this time, I think it also is appropriate to recognize Margaret Stevenson, who has worked tirelessly on behalf of myself and my partners. The success of her efforts perhaps can be measured by the fact that, over the years, I am the fourth from her office for whom she has helped to prepare a presidential address for a major thoracic surgical association.

Finally, and most importantly, I would like to thank my wife, whose love and support throughout the 39 years of our marriage have made it all worthwhile.

Philosophy 1

In my second year in college, there was an opening in my busy 3-year premedical curriculum, so I took a course labeled Philosophy 1. By this I hoped to broaden my educational experience, as it seemed that botany, zoology, mathematics, chemistry, embryology, comparative anatomy, and similarly oriented courses were occupying an adequate portion of my time. In the first session of Philosophy 1, the entire hour consisted of a definition of the term *philosophy*. I must confess that I really didn't understand the meaning of the word even after the lecture. At the completion of the semester (I think I wrote an "A" in the final examination) I took the professor aside and asked him to, again, "briefly" define philosophy for me. This definition took only 15 to 20 minutes, and I still didn't completely understand what he was talking about.

After reviewing my thoughts for this presentation, it seemed to me that the same situation might well obtain for my audience. The title of this address is entirely appropriate because it serves to remind me to keep my message, which is in large part philosophical, as understandable as possible.

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

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Fig 1. Dr Hiram T. Langston.

What is Happening?

All of us are aware of trends and events in recent years that are changing our profession. Medical care is coming to be regarded as a salable commodity, the delivery of which is expected to be a guaranteed right to every citizen, and the price of which is negotiable and controllable by fiat from local, state and federal governments. Such caveats as quality of caring and dedication to the honorable science and art of medicine, first penned by Hippocrates, are noticeably absent from deliberations and treatises regarding us. In the last 20 years or so, this lack of concern has been ascribed almost universally to physicians and surgeons in general.

Does recent history contain a reason or reasons for this loss of prestige by our profession? I think it does. My views are simplistic, but in that is virtue because there is no formal discussion of this presentation and simple views are more often accepted without statistical support of the inferences.

The three obvious things, in my view, that have contributed to our changing image are (1) the cost of medical care, (2) public funding for almost everyone, and (3) involvement of government in the practice of medicine.

Increased Cost of Medical Care

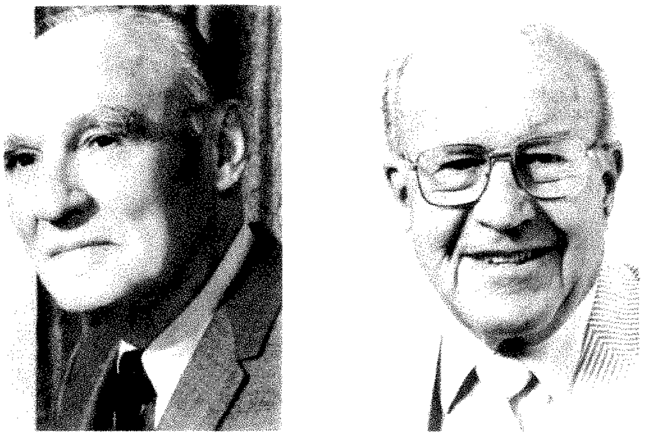
Costs of medical care have increased substantially since our Society was founded. Does this increase parallel the changes that have occurred across the board in our economy? Here are some noteworthy comparisons. In 1963, a loaf of bread cost 21 cents; today it is $1.39, a sixfold increase. A two-bedroom home in Los Angeles cost $15,000 then; today it is $150,000. Twenty-five years ago the median income in California was $2,973 per year; today it is $24,000 per year—again a nearly tenfold increase. In 1963, in our practice an open heart operation cost $2,500, and today a comparable open heart operation is $6,200. Our charge has increased by a factor of a little more than two. At our hospital, however, the daily room rate over 25 years has changed from $20 to $450, a more than 20-fold increase. (Last week, we received notice from our hospital that the room rate will be increased again—to over $500.) Because our hospital, like others, is a "not for profit" institution, this is principally an increase in the expense of doing business and is primarily related to labor costs and the cost of new technology, and has little to do with profit.

Information from the Health Care Financing Administration clearly demonstrates that, since 1950, the fraction of national health care expenditures allocated to physicians' services has actually decreased from 21.7% to 20.5% (Fig 3). It is interesting to note that there has been a rather marked increase in expenditures for hospital and nursing homes from 32% to 47%.

Basically, the data support my contention that the increase in physicians' fees has substantially lagged behind the increased cost of living which, presumably, has followed inflation. In fact, in our practice the charge for surgery has increased at a much slower rate. The government's figures showing the mounting expense of Part B of Medicare must, therefore, be related in large part to the increase in volume of service and administrative costs.

Public Funding

A second major factor influencing the public's perception of our profession has been the assuming by the federal and state governments of the responsibility for funding of patients' medical care under the Medicare and Medicaid programs, which were enacted in 1965. These programs, by providing payment for most patients, have removed from the physician the altruistic and ethical incentive to care for the poor at a reduced fee or for no charge. This very honorable tradition of our profession was also prescribed by Hippocrates, and, for those of us who have been in practice for more than 20 years, it was an easily recognizable part of our activities. In recent years, however, the provision of medical care without charge is almost nonexistent in the private hospital, and even in county and municipal charity institutions fees are collected from Medicare and Medicaid for a high percentage of patients.



A B

Fig 2. (A) Dr John C. Jones and (B) Dr Bert W. Meyer.

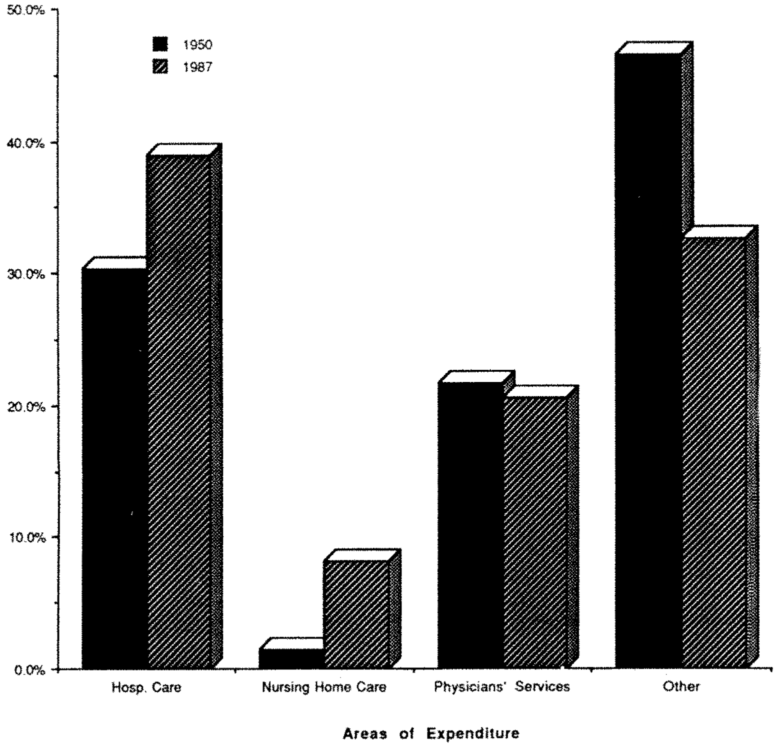


Fig 3. National health expenditures by type. (Source: Health Care Financing Administration.)

Involvement of Government in Medical Practice

Closely related to, and basically the result of, public funding is the third factor that has had a major impact upon our profession. This has been the involvement of political agencies in the conduct of a previously private business. The budgetary projections for Medicare expenditures, which were made in 1964 and 1965, have been exceeded by an enormous margin. These increases have been so great on a national level that the budget for Medicare and Medicaid is now exceeded only by that for national defense.

This excess of current expense compared with projected expense is understandable, and is based primarily on inaccurate predictions of utilization. The development of new procedures applicable to a large number of patients in the Medicare age group (such as eye lens implantation and coronary artery surgery) and the expense of new technologies that are now standard practice (such as computerized axial tomographic scans and magnetic resonance imaging) have contributed to the inaccuracies of these earlier predictions. The increase in cost for malpractice insurance has also played a substantial role in the increased expense. The major factor, however, has been the volume of patients using medical care and the volume of services used per patient.

Another factor, not often mentioned, that has added substantially to governmental budgetary problems has been the rapidly growing, enormous expense to government that has proved necessary simply to administer such a large program at the national level. This administrative expense is added to the actual cost for service, and becomes an integral part of the bottom line of federal expenditure for physician services.

In a thus far unsuccessful attempt to restrain the rapid growth of medical expense to the government, politicians have forced health professionals into a competitive marketing posture to maintain fiscal solvency. Government agencies and the courts have done this by condoning and encouraging competitive marketing techniques that the profession has always classed as unethical.

Public funding and the intrusion by political agencies into the conduct of the practice of medicine have forced the physician into the political arena where he or she can be easily portrayed by adversaries as being a "money-grubbing," "noncaring" opponent of the "public good." In this arena our public proclamation of the moral, ethical, and well-intentioned motivation for our activities is easily dismissed as self-serving and therefore untrue.

The philosophy of these concepts is strengthened by the following quotation from Albert R. Jonsen, PhD, the well-known ethicist.

> One need not be an ethical genius or saint to recognize that marketing health care compromises one of the most fundamental principles of ethical practice. In the words of the Hippocratic text, "Should someone in financial straits require service, give it fully, for where there is love of humanity, there is love of the art."
>
> Competition as the spirit of medical and surgical care erodes the compassion that has always been medicine and surgery's highest virtue . . . I know the issues are complex; I know they are made even more complex by the litigious spirit which is, by the way, a natural consort of the competitive spirit. But at the same time, I am reasonably sure that competition will lead to greater exclusion of those persons who will not be profitable patients and to greater solicitation of those who can be induced into being patients. The first will be deprived of needed surgery; the latter will be the victims of fashionable surgery [1].

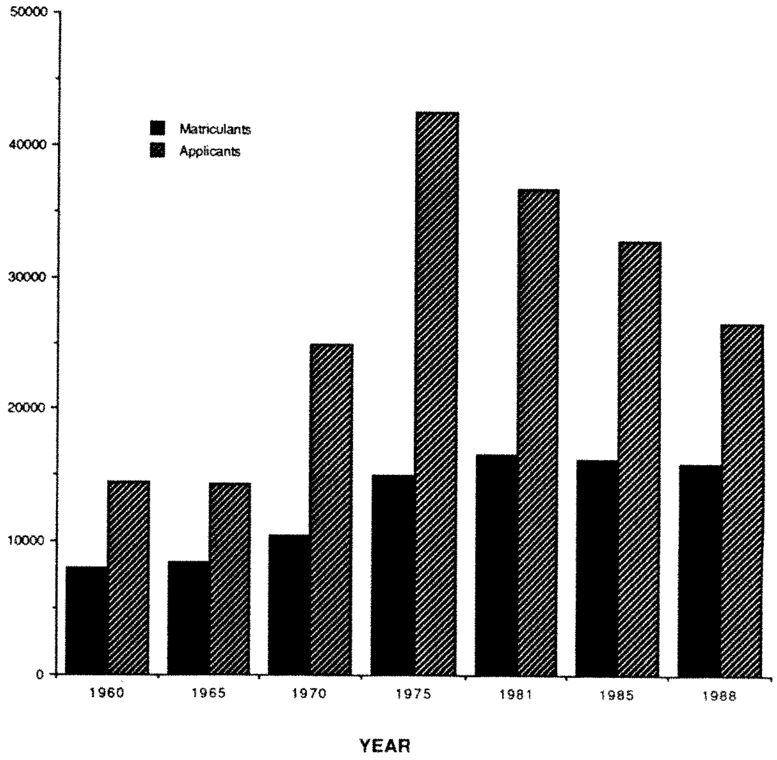


Fig 4. Number of medical school applicants and matriculants by year. (Source: Director of Admissions, Harvard Medical School.)

We should heed this warning and consciously work to prevent the fulfillment of this prophecy.

What Are They Doing to Us?

We have a tendency to incriminate agents when we are struck by adversity. This is after the fashion of Alexander the Great, who would kill the messenger if he bore bad news. For the increasingly negative events related to our profession, as physicians we tend to lay the blame on the lawyers, the politicians, and the bureaucrats. In my opinion, however, the blame does not rest solely with these groups, but rather also on the population in general, including us, our patients, and those who will one day become our patients. After all, in this country, public policy and opinions are still a product of the will of the people. Why then are governmental agencies, third party payers, the courts, and others increasingly acting to our disadvantage?

One obvious answer to this question, in my view, is simply that these actions are rewarding to them and are allowed by public opinion. What forms public opinion about us? The answer to this seems clear. Public opinion about any group, when the public is free to form an opinion, is based primarily on the perception by people in general of how the group performs and behaves. In the case of our profession, this perception stems from how we act collectively but, perhaps even more importantly, it is based on how we act individually.

In today's market, we are being forced inexorably to behave more and more like the street peddler haggling over the price of his or her merchandise. This type of activity, at the very least, tarnishes our image of being caring physicians. It influences the public's perception of our profession, and we, the public, allow the politicians and bureaucrats to deal with us as if we were street peddlers. This perception is obviously incorrect.

Can We Influence Change?

Can we, as a specialty, influence and direct changes that are occurring and will continue to occur to our profession? I think the answer to this question is yes.

The politicians and the bureaucratic maze supporting them are the policy makers and, by virtue of their positions, they are subject to political pressure. Political pressure is most effective (as it should be) when it is exerted by the electorate in general. If the electorate can be made to understand us, our work, and our concerns regarding the future of our profession, the political clout of that understanding would be enormous. The popularity and esteem that the public still accords our profession and our specialty are certainly far greater than that given to those groups that we historically have incriminated, that is, the lawyers, politicians, and bureaucrats. We are privileged to have daily communication with patients and friends who listen to and respect our opinions. We must continue to use these interchanges to express our concerns regarding the effects national policy changes will have on the quality of their medical care.

The effects these changes have already had on our profession are perhaps best demonstrated by the data from the Director of Admissions at Harvard Medical School (Fig 4). The number of individuals being enrolled in our nation's medical schools has not shown a significant change over the last 15 years. However, the number of applicants has been going down over the past 15 years,

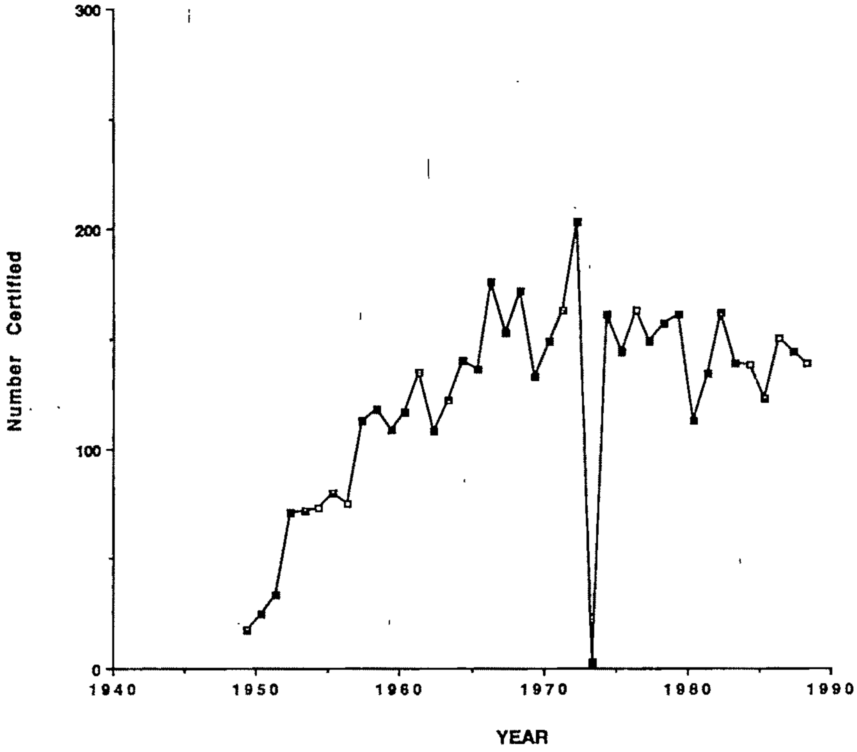


Fig 5. Number of thoracic surgeons certified each year from 1949 to 1988. (Source: The American Board of Thoracic Surgery, Inc.)

so that the ratio of applicants to positions has changed from 2.8:1 in the mid-1970s to 1.7:1 in 1988.

Data from the US Bureau of the Census show that over the past 17 years the total number of surgeons has increased by only 30% per 100,000 population, while the number of primary care physicians has increased 43% per 100,000 population [2]. The increase in thoracic surgeons per 100,000 population has been less than 20% during the same time. This is not surprising when one sees that the number of surgeons annually certified by our Board has remained at about 125 to 150 per year for the last 25 years (Fig 5).

Projections from the US Department of Health and Human Services show that by the year 2000 the number of thoracic surgeons will increase by only 15%, whereas family care physicians and cardiologists will increase more than 35% (Table 1). Even though the average income for primary care physicians is substantially less than that for thoracic surgeons, young physicians are obviously not crowding into our specialty for financial reward.

Table 1. Manpower Projections

	Year		
Specialty	1988	2000	% Change
Primary care	225,311	303,420	+35
Cardiologists	14,590	21,190	+50
Thoracic surgeons	2,085	2,390	+15
Total physicians	546,296	708,600	+30

Source: Bureau of Health Professions, US Department of Health & Human Services.

Over the past year "thoracic surgery" has been attempting to assist governmental policy makers by providing them with continuing consultation and information regarding our specialty. We have made these efforts through a cohesive structure representing all of the four major thoracic surgical associations, coordinated through an ad hoc committee of The Society of Thoracic Surgeons. This committee, chaired by Dr George Miller, has worked tirelessly on our behalf. The efforts have been effective in the short term by tempering and limiting changes that, in the long term, would be extremely damaging to our specialty. The motivation for this activity is, however, poorly understood, and as the activities have been primarily related to reimbursement, the prime motive can easily be labeled as self-serving and self-enriching.

Having worked closely with this committee for more than 1 year, I can assure you that, judging from my own pocketbook, self-enrichment has not been a factor in stimulating the members of this committee in their time-consuming efforts. Rather, it is the future of our specialty that is the prime stimulus. In a free enterprise, capitalistic system monetary reward is honorably and rightfully one of the major factors that directs a person toward career selection. If financial compensation for thoracic surgery is substantially reduced, the quality and caliber of individuals attracted to our specialty will likewise be substantially reduced. The effects of such a change, of course, will not be reflected in patient care for a period of at least 10 to 15 years. Logically, it follows that such a change possibly, and probably, would have an adverse effect on the quality of care for our patients.

To attenuate such adverse change to the future of our specialty has been the prime motivation for my work in

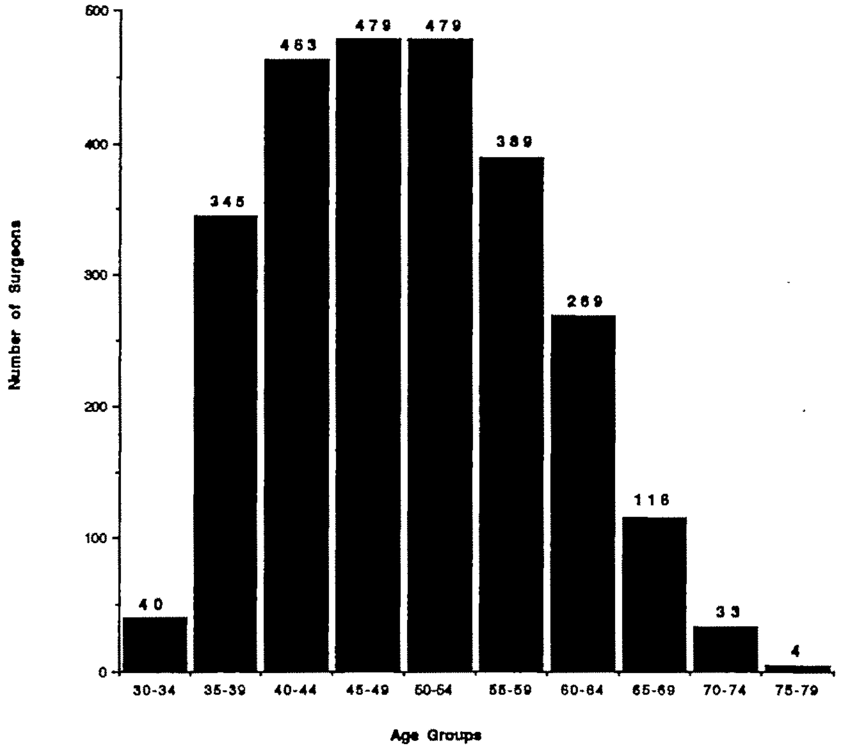


Fig 6. Number of board-certified thoracic surgeons in active practice by age group in 1985. (Source: Thoracic Surgery Manpower, Fourth Manpower Study of Thoracic Surgery.)

this arena, and I am certain that this motivation applies to the entire committee working on your behalf. I urge you to continue your wholehearted support of such activities.

Thoracic Surgeons

Finally, I would like to tell you some things about thoracic surgeons. Most of these are platitudes that we all know, but generally do not vocalize because it certainly would sound self-aggrandizing. As your President, however, I can appropriately say these things about you, and I am proud to do so.

Thoracic surgeons are good, honest, intelligent people. I have associated with many of you throughout my career, and you deserve trust and respect. You have mine. I am sure your friends and patients hold you in similar regard.

You are caring people. You care about your patients. On a daily basis you spend hours struggling to preserve a patient's life or to enhance a patient's life-style. You feel enormous personal gratification when you achieve success in these endeavors.

You care about your profession. You regularly read and attend meetings and communicate with your peers to keep yourself informed about advances that are being achieved in our specialty. Your life-style and reimbursement are appropriate rewards. In a capitalistic society, the value of service is established by the marketplace. In my view, the marketplace has worked.

The work intensity commitment and the educational requirements that you voluntarily enforce are severe, but they are poorly understood even by other medical professionals, and even less by politicians, bureaucrats, and the general population. Let me enumerate some of these facts. They are well known to us, but others need to understand.

1. The average thoracic surgeon cannot complete his or her training and begin practice before 35 years of age. No other profession requires this much time in training. Data from The Society of Thoracic Surgeons Manpower Study show that the average age of the practicing thoracic surgeon is 50 years (Fig 6). Most have stopped practicing by age 60 years. Thus, 29 years of formal education lead to a productive career that averages less than 25 years (83% of practicing thoracic surgeons are under 60 years of age).
2. Surgeons between 35 and 54 years of age perform 85% of all *cardiac* operations in the United States. Overall, 75% of all *thoracic* operations are performed by surgeons between 35 and 54 years of age [3].
3. The voluntarily assumed work commitment of a thoracic surgeon is heavy. Ten- to 12-hour work days are not unusual. To evaluate the intensity of the work you perform, one has only to measure the blood pressure of a thoracic surgeon during a difficult case. This stressful intensity can also be observed in a thoracic surgeon when one of his or her patients does not survive. The frequency of this stress can be appreciated if we realize that, in cardiac surgery in general, approximately 1 of every 15 patients we try to help does not survive our carefully planned, but overt intervention. The frequency of this severely disheartening result is experienced by no other profession. Conversely, we do realize that frequently our interventions can convert a patient who is dyspneic at bed rest to a patient who can conduct a meaningful, useful life.

4. I have tried unsuccessfully to obtain actuarial data about the life span of thoracic and cardiovascular surgeons, but I am sure that if this information is available, the energy and emotional drain demanded by your specialty are rewarded by a shortened existence.
5. This Society, which you formed 25 years ago, functions to advance the knowledge and skill of our specialty and to enhance the ability of our specialty to deliver quality patient care. The major thrust of our Society has been and will continue to be education and dissemination of new scientific knowledge related to our specialty. The thirst and need for this is manifested by the large attendance at these meetings. This dedication can be better understood when we realize that over 100 actively practicing thoracic surgeons serve on the committees and councils of our Society, addressing all facets of our specialty. These busy surgeons provide thousands of man-hours of work for which they are not compensated. All of your programs are supported by you, the members, and are not subsidized by government in any form.

Finally, I offer this quotation attributed to Thomas Carlyle (1795–1881): "I do not believe in the collective wisdom of individual ignorance." This philosophy of Carlyle is far reaching. We must do our best to understand the workings of the social, economic, and political environment in which we exist. With this understanding, we must attempt to constructively influence and, when appropriate, instigate the constantly occurring changes.

In my opinion, thoracic surgeons are good, highly trained, appropriately motivated individuals who provide a caring, quality service that is of great value to our patients. We must continue to struggle collectively and individually for as long as is necessary to preserve the quality, integrity, and honor of our specialty. We must combat and refute utopian engineering by governmental bodies and well-meaning individuals who have little understanding of the complexity of our specialty, the intensity of our work, or, for that matter, the needs of our patients. I hope my presentation of well-known facts about us and our philosophy will be of use in that struggle.

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Technical and Scientific Advances in General Thoracic Surgery

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The purpose of this report is to identify some of the major advances in noncardiac thoracic surgery during the first 25 years of The Society of Thoracic Surgeons. To place this discussion in perspective, it is necessary to consider the state of our specialty at the time of the founding of The Society in 1964. The origins of the specialty of modern thoracic surgery began after World War I when management of the pleural space and the technique for endotracheal positive-pressure anesthesia became widely known. The decade of the 1930s saw the introduction of most of the major pulmonary and esophageal resection techniques. After the first successful pneumonectomy reported by Graham and Singer [1] in 1933, resectional lung surgery progressed rapidly so that the ultimate anatomical unit of segmental resection was employed clinically by Churchill and Belsey [2] and reported in 1939. Also during this decade, esophageal resections evolved rapidly from the successful use of esophagectomy without thoracotomy by Grey Turner [3] to the successful one-stage transthoracic resection and reconstruction accomplished in Japan by Ohsawa [4] in 1933 and introduced in the Western world by Adams and Phemister [5] in their 1938 report.

Interrupted by the second World War, the quarter century from 1939 to 1964 saw numerous technical surgical advances in pulmonary, esophageal, and mediastinal surgery although mortality and morbidity rates remained high. The beginning of open heart surgery in the 1950s opened another era in our specialty, which is described in a separate report by Kirklin [6]. A few fellowships in the newly emerging specialty of thoracic surgery began to be offered in the 1930s [7, 8], and formal training programs were introduced after World War II leading to the establishment of the American Board of Thoracic Surgery in 1948.

At the time that our Society was founded, the body of knowledge concerning the diseases, surgical techniques, and educational programs defining thoracic surgery was well established. The stage was set for the next quarter century to achieve remarkable technical refinements in the operating room, greater sophistication in diagnosis and preoperative and postoperative care, and fundamental advances in the understanding of the pathophysiology of thoracic surgical diseases and their complications. The results have been a remarkable lowering of the risk of thoracic surgery and the extension of its techniques and principles to a broader range of ill patients with a greater variety of diseases.

As this is principally a celebration of the North American-based Society of Thoracic Surgeons, in preparation for this report I reviewed publications in the two major North American journals of our specialty, *The Annals of Thoracic Surgery* and *The Journal of Thoracic and Cardiovascular Surgery*, during the past 25 years. More than 200 identifiable technical or scientific advances could be culled easily from these two journals. The major advances tended to cluster in particular fields and are grouped by category.

Those advances that introduced basic concepts of pathophysiology or fundamental mechanisms of treatment are accorded greater importance, and those that affect larger numbers of patients also receive higher priority in this review. The presentation that follows is purely arbitrary and solely reflects my viewpoint. Fifteen major categories of advancements are presented without great concern for rank ordering. Thereafter a number of other advances are described in less detail. Finally some efforts are noted that have not yet proved successful and remain problems or opportunities for the future.

Thoracic Surgical Infections

Comparison of thoracic surgical practice from the previous quarter century to the present immediately brings into focus the radical changes that have occurred in treatment of intrathoracic infectious diseases. Obviously, this reflects in large measure the continued remarkable advances in the development and understanding of the uses of antibiotics. Surgical resections for tuberculosis, cavitating fungal diseases, and bronchiectasis were still a common, albeit declining, part of thoracic surgery during my residency in the first half of the 1960s. Today such resections are rare and thoracoplasty is almost a forgotten art. Although tuberculosis is far from eradicated in North America, the availability of specific antibiotics for most varieties of the disease largely eliminates the need for lung resection. Tuberculosis empyema and pericarditis are still encountered, and there is concern that drug-resistant organisms will lead to a future recurrence. Acquired bronchiectasis, on the other hand, seems largely to have disappeared, quite possibly as a result of widespread diphtheria-pertussis-tetanus inoculations in childhood as well as antibiotics.

A fundamental advance in thoracic and other forms of surgery is the understanding of the proper use and effectiveness of prophylactic antibiotics as worked out by Burke and others [9–11]. Preoperative and intraoperative use of antibiotics against potential contaminating organ-

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isms leads to a marked reduction in the incidence of postoperative infections, and the short-term use of antibiotics avoids overgrowth of resistant organisms.

Management of empyema and lung abscess was a major concern 25 years ago, but is greatly improved by the availability of specific antibiotics and simplified methods of drainage such that rib resection and open drainage or thoracoplasty for empyema are rarely required. Indications for early decortication of extensive empyema are established [12, 13]. Pulmonary resection for lung abscess, a highly risky undertaking, is almost never necessary today. The use of closed drainage of the pleural cavity combined with appropriate antibiotics, irrigation and then closure of the antibiotic-filled postpneumonectomy space [14], and endoscopic [15] or percutaneous drainage of lung abscess [16] coupled with vigorous pulmonary physical therapy make major operations for these conditions generally avoidable. Follow-up shows that a residual cavity after a lung abscess is fully drained and sterilized with antibiotics does not forecast recurrent infections or require resection.

However, mankind's battle with infectious organisms continues, so the thoracic surgeon continues to play an active role in the diagnosis and treatment of newer manifestations of infectious diseases. Problems in diagnosis in the immunosuppressed patient frequently require the services of the thoracic surgeon for endoscopic, percutaneous, or open pulmonary biopsy for both tissue and culture [17, 18]. Aspergillosis, candidiasis, and other fungi in old cavitary disease causing hemoptysis lead to the need for resection in some cases]19]. Bronchial arterial embolization may stop hemorrhage in some instances [20]. The rapid spread of acquired immunodeficiency syndrome in this decade makes the thoracic surgeon much more familiar with *Pneumocystis carinii* pneumonia and its diagnosis and treatment [21, 22], along with a variety of other infectious diseases considered exotic rarities 25 years ago. Changes in the spectrum of thoracic surgical infections are remarkable, with great progress made in several fields and the emergence of new problems for the future.

Endoscopy

Rigid-tube bronchoscopy and esophagoscopy were central in the education of the thoracic surgeon in the 1960s. In fact, the residency at Massachusetts General Hospital devoted an entire 2-month rotation just to this subject. Introduction of fiberoptic technology to endoscopy in the 1960s led to remarkable advances in the diagnosis and treatment of bronchial and esophageal disorders with a substantial reduction in risk and discomfort to patients [23, 24]. However a secondary effect of the ease by which fiberoptic bronchoscopy and esophagogastroscopy can be done is the widespread adoption of this technology by nonsurgeons in related medical and pediatric disciplines [25]. An unfortunate outcome is a drastic reduction in endoscopic experience with both rigid and fiberoptic endoscopes available to the thoracic surgery trainee, with a concomitant reduction in his or her visualization and derivative understanding of the pathological processes.

The ability to obtain brushings and biopsy specimens of actual lung tissue and selective cytological samples of infectious or neoplastic diseases provides great accuracy in the diagnosis of many diseases [26, 27]. The recent addition of ultrasonic technology to esophagoscopy is already providing highly sensitive evaluations of the wall penetration of esophageal malignancies and presence of enlarged lymph nodes [28].

Fiberoptic technology extends therapeutic as well as diagnostic applications of endoscopy. Transbronchial lavage for pulmonary alveolar proteinosis and other conditions is well established [29]. The ability to dilate bronchial and esophageal strictures by way of inflatable balloons passed endoscopically offers alternative managements for these conditions [30, 31]. Recently laser application through the endoscope introduced a new approach to the palliation of strictures and malignant obstructions in both the bronchus and the esophagus [32, 33]. Photodynamic therapy combining laser endoscopy with drugs that sensitize malignant cells is in an early stage of evaluation with some encouraging initial results in bronchogenic carcinoma [34] and proximal pharyngeal and esophageal neoplasms [35]. Without doubt technological advances will continue at a rapid rate in the years ahead, and fiberoptic endoscopy will prove to have been one of the major milestones in the advancement of diagnosis and treatment of thoracic diseases.

Anesthesia and Critical Care

Hospital mortality rates for major pulmonary and esophageal resections have declined as much as fivefold in the past quarter century. The risk of pneumonectomy and lobectomy is now in the range of approximately 5% or less [36, 37], and recent reports indicate that current mortality for esophagectomy is in the same range [38].

Much of the credit for this remarkable improvement in outcome relates to a number of important advances in anesthesia and postoperative cardiorespiratory care. Respirators are more sophisticated, and the importance of positive end-expiratory pressure and the role of constant positive airway pressure are widely known [39, 40]. Intraoperative monitoring including the use of the Swan-Ganz catheter for pulmonary wedge pressures [41], CO_2 monitoring [42], noninvasive methods for capillary oximetry [43], and other monitoring techniques are major advances. These permit the introduction and safe use of single-lung anesthesia [44] and high-frequency jet ventilation [45, 46] which considerably extend the operative techniques available for unusual or difficult pulmonary or esophageal disorders. In parallel, a number of safe and highly effective anesthetic and cardiovascular support drugs are widely used. The days of ether, cyclopropane, or nitrous oxide with curare of the 1960s are long gone. The highly specialized and skilled cardiothoracic anesthesiologist is now not only a welcome but an essential member of the thoracic surgical and intensive care team.

Nutrition

Particularly in cases of debilitating benign or malignant esophageal obstructions or the complications of esophageal operations, the introduction of total parenteral nutrition [47] and the evolution of understanding of its components in recent years are major advances. Previously life-threatening situations can now be handled routinely with the expectation of successful outcome. Advances in technology and nutritional therapy enable home treatment of patients with total diversion of the upper digestive tract by either intravenous or enteral total nutritional management. Important variables for preoperative evaluation of nutritional status are established and used routinely to select high-risk patients for nutritional preparation before major thoracic procedures [48, 49].

Management of Gastroesophageal Reflux

In the 1950s, Belsey [50], Collis [51, 52], Lortat-Jacob [53], Nissen [54], and others developed techniques for the correction of esophageal reflux after Allison [55] correctly identified reflux as the cause of esophagitis and symptoms previously attributed to hiatal hernia. Although the techniques for antireflux surgery were being developed, their evaluation and use in North America began in the 1960s and other methods such as the Hill repair [56, 57] evolved since.

During the first 10 years of our Society, the development of esophageal function tests took place, including the standard acid reflux test [58, 59], the acid clearing test [60], prolonged pH monitoring [61, 62], quantitative esophageal manometry [63], and, more recently, prolonged esophageal manometry [64, 65]. The tests offer objective methods for measuring the severity of reflux and the underlying defects, guiding the indications for operation and the application of specific types of antireflux procedures tailored to the abnormality identified in the individual patient, and measuring surgical outcomes.

From intensive research using these techniques in the past 25 years, the principles that govern successful antireflux operations are now identified [66] and include not only the intrinsic muscle tone of the distal esophagus, but location of this distal esophageal tube within a positive-pressure environment [67–70], and the role of the Law of Laplace [71] in creating a barrier to reflux between the esophagus and stomach by calibration of the smaller diameter swallowing tube entering abruptly into the larger diameter gastric sac. These factors are now known to be critical components of the successful antireflux repairs, the effectiveness of which is established by long-term follow-up including quantitative evaluation [72–75].

Antireflux surgery has evolved from a new concept replacing hiatal hernia repair 25 years ago to a field that now has well recognized indications for operation and operations that, although not 100% effective, have outcomes that are well known and complications that can be predicted or avoided.

Of great interest is the emergence of the columnar lined esophagus (Barrett's esophagus [76]) as a problem occurring in substantial numbers of patients in recent years and with a high premalignant potential [77, 78]. Much current research that will bear fruit in the years ahead is focused on the malignant transformation and treatment in this disease, an unusual opportunity to study the neoplastic process in humans.

Fig 1. Ronald H. R. Belsey, MS, FRCS, pioneering cardiothoracic surgeon whose innovations span 50 years [2, 79] across the entire specialty: an educator whose "School of Esophageal Surgery" has profound influence in North America and worldwide and made esophageal surgery a real discipline.

This has been a remarkable quarter century in esophageal surgery overall, which has expanded successful treatments to large numbers of patients with diseases previously incurable or of great risk. Much of the credit for the establishment of esophageal surgery as a subdiscipline of the specialty must go to Ronald Belsey (Fig 1), who not only introduced a number of the successful techniques currently employed, but shared his knowledge by training as Registrars and Fellows a large number of North American and other surgeons who are making major contributions to the further advancements of esophageal surgery. Belsey's contributions cover the entire spectrum of cardiothoracic surgery and incredibly span a full 50 years from 1939 [2] to the present [79].

Tracheal Resection and Reconstruction

Prior to 25 years ago extensive tracheal resection and reconstruction was uncommon [80, 81]. The use of prosthetics continues to be disappointing. The work of Grillo [82–84] and others [85] over the quarter century establishes the principles and techniques that make extensive tracheal and cervical resections with primary repair a standard part of the thoracic surgical armamentarium. Unfortunately, many patients requiring tracheal resection did so because of injuries from high-pressure and ill-fitting balloon cuffed endotracheal or tracheostomy tubes [86–88]. Another major contribution is the development of a low-pressure cuff for tracheostomy and endotracheal tubes, which substantially reduces postintubation tracheal stenoses or tracheal malacia requiring resection [89, 90].

Cancer Chemotherapy and Combined Adjuvant Treatments

In 1966, Huggins became the most recent surgeon to be awarded the Nobel Prize, in this case for developing the concept that hormones and drugs alter the progression of cancer. During the past quarter century a large number of drugs have been tested for antineoplastic effect, and a number of trials carried out. Although the results for lung and esophageal cancer are not yet as good as one hopes they will be, some achievements of chemotherapy are sufficiently impressive that this concept must rank among the top advances.

Prior to the 1970s, the results of treatment for small cell carcinoma of the lung were dismal [91]. For this lung cancer chemotherapy has dramatic effects, and a number of patients now achieve long-term survival [92, 93]. The results were initially so much better than surgical resection that small cell carcinoma was regarded for a time as a nonsurgical disease. More recently the concept of combining operation after a chemotherapy response is achieving creditability [94, 95].

For other specific neoplasms such as germ cell tumors, primarily in the mediastinum or metastatic from the testes or other sites, and sarcomas, chemotherapy is giving remarkable results [96–98]. The extension of thoracic surgery to remove carcinoma metastatic to the lung from certain neoplasms after chemotherapy is now commonplace [99, 100]. The potential of combinations of operation with preoperative or postoperative chemotherapy and preoperative or postoperative radiation therapy for other kinds of neoplasms attracts much attention in thoracic surgery oncology at present.

The role of preoperative chemotherapy with or without radiation therapy is being investigated intensely for esophageal and lung carcinomas [101]. The results in those patients who have a complete response are encouraging, but an overall effect in prolonging life for the population of patients with these diseases is not yet established [102, 103]. Although the potential is exciting, it must be recalled that 25 years ago there was great interest in preoperative radiation therapy for lung and esophageal cancer [104, 105]. Long-term evaluation now shows that there is no survival advantage from preoperative radiation over primary surgical resection reserving radiation therapy and/or chemotherapy for later postoperative recurrences should they occur [106, 107]. Much is known about the dosage and combinations of drugs available that reduces the toxicity and complications of combined therapy. Undoubtedly substantial advances will be achieved in thoracic surgical oncology in the quarter century ahead, but the enthusiasm for new adjuvant therapies must be tempered by concurrent controls of primary surgical resection, which still remains the proven standard.

Staging for Lung and Esophageal Carcinomas

The pathological staging of lung cancer, and particularly esophageal cancer, in recent years is much more sharply defined and now correlates well with prognosis after treatment [108]. The introduction of a variety of methods for treating lung and esophageal cancer places emphasis on the selection of patients for either curative or palliative treatment. For these reasons, importance is placed on improving clinical staging [109]. A number of techniques are evaluated, and in combination lead to substantial ability to stage lung and esophageal neoplasms preoperatively, thereby influencing the choice of therapy. The era of the metastatic bone survey, alkaline phosphatase measurement, chest roentgenogram, and possibly scalene node biopsy of the 1950s and 1960s has given way to considerably more sophisticated technology [110, 111].

Computed tomographic scanning and magnetic resonance imaging substantially increase the visualization of the tumor region and enable us to select out patients with more advanced disease [112–117]. The impact is a reduction in the numbers of patients who are explored for thoracic neoplasms and found to be unresectable who do not benefit from the operation. Mediastinoscopy, initially introduced in the late 1950s but not receiving widespread attention until a decade later [118, 119], (and mediastinotomy [120] for left hilar tumors) proves highly useful in the preoperative staging of lung cancer. Radionuclide imaging, including the bone scan, liver-spleen scan, and gallium scan are evaluated for tumor staging, but contribute only occasionally to the identification of unsuspected systemic disease [121–123]. Fine needle aspiration biopsy of nodules identified by computed tomographic scan is an advance in clarifying the nature of the suspicious nodule without the need for excisional biopsy [124]. The addition of ultrasonography to esophagoscopy shows great promise for local staging of esophageal carcinoma, but is still under evaluation [28]. Because of the importance of staging not only for selecting patients for different types of treatment, but for comparing of outcomes of competing types of therapy, there will undoubtedly continue to be great interest in this field of investigation in the years ahead.

Surgery for Lung Cancer

Although most of the widely used resections of bronchogenic carcinoma were well known before 1964, there continues to be improvement in technique and the extension of established operations for new indications. The earlier observations of Paulson [125] concerning the potential curability of some patients with the superior sulcus (Pancoast) tumor are confirmed by others [126]. The extension of surgical resection to this disease previously thought to be incurable yields surprisingly good results in patients with localized tumor. Newer techniques for chest wall reconstruction, including major flaps [127] and "sandwich" prostheses [128], permit extension of resection and long-term salvage to patients with chest wall invasion previously thought to be inoperable.

Conservation of lung tissue is another theme in recent years that permits resectional therapy in patients with marginal pulmonary function or previous thoracotomies. Bronchoplastic resection [129, 130] and the observation that anatomical segmental resection can be curative for small carcinomas are newer trends in this area [131]. Median sternotomy for the removal of bilateral nodules simplifies the surgical procedure and morbidity for treatment of this condition and allows such resections in more patients with surprisingly prolonged survival on occasion [132, 133]. For patients found to have unresectable primary or secondary pulmonary carcinoma interstitial radiation implants are being evaluated and show promise in individual cases [134].

The greatest public health advances in thoracic neoplasia are the widespread acceptance of both asbestos and tobacco as carcinogens and a concerted public effort to reduce exposure to these substances.

Chest Trauma

Principles for managing chest trauma were well established before the Vietnam War, but improvements in the techniques for resuscitation from shock [135], autotransfusion [136], and sharpening of the indications for thoracotomy versus supportive therapy with drainage for penetrating and blunt chest trauma resulted from the Vietnam [137] and subsequent urban trauma experiences [138]. In addition to the specific management of the chest lesion, considerable knowledge is being acquired in the causes of adult respiratory distress syndrome [139, 140] and its relationship to sepsis [141]. Although this still causes high mortality and is not fully resolved, important steps are being made to improve understanding and treatment of this condition [142, 143]. The role of extracorporeal membrane oxygenation in acute pulmonary failure is a current major focus of investigation and promises to become established as a major advance [144–147].

Additional Major Advances

The popularization by Heimlich of the maneuver to dislodge aspirated food and its widespread public dissemination is undoubtedly a major advance in public health and the saving of life [148].

With the documentation that operation is curative for early neoplasms of the lung, esophagus, and stomach, efforts at early detection are being refined and employed on a population-wide basis in several centers [149, 150]. Results indicate that presymptomatic neoplasms can be detected by cytological means [151–154]. Identification of high-risk groups in which the cost of mass screening is justifiable is the next step in widening the benefits of this advance. Cytological screening of sputum is currently indicated in smokers with previously treated head and neck and foregut neoplasms, and esophageal brush cytological examination is similarly indicated in such patients and those with Barrett's esophagus or previously treated caustic esophageal strictures.

Esophagectomy techniques are being refined and adapted to specific indications for curative or palliative treatment. Esophagectomy without thoracotomy has been reintroduced in Japan by Akiyama and associates [155] and subsequently in North America by Orringer and Sloan [156] and others. This proves as safe as transthoracic esophagectomy for palliation of esophageal carcinoma [157] and may have advantages in patients with poor pulmonary function or previous thoracotomies. Patients with early lesions may achieve long-term survival. The concepts of en bloc cancer resection have been extended to the esophagus in recent years and carried out without increased mortality or morbidity [108, 158, 159]. This technique appears indicated in patients with potentially curable tumors and gives the most complete control of local disease as well as the most thorough staging of the neoplasm with implications for postoperative adjuvant therapy. In recent years the trend in esophageal surgery is toward one-stage rather than multistage procedures as previously practiced. Transthoracic esophagectomy without laparotomy for middle third carcinomas offers a method for reducing the morbidity in select patients [160].

Lung transplantation and heart-lung transplantation for patients with bilateral pulmonary disease is emerging as an effective procedure and will undoubtedly be much more widely practiced in the near future [161–165]. A number of technical advancements contribute to the current success of this operation, frustratingly long in coming compared with transplantation of other organs [165–167]. Among the advances is the use of omentum or other tissue to buttress the tenuous and poorly vascularized bronchial or tracheal anastomosis [168]. Specific indications for the selection of patients and results in sufficient numbers to assess the value of lung transplantation remain to be reported, but the procedure is now technically and biologically feasible and will increase substantially in importance as a major advance.

Most types of esophageal reconstruction were introduced before 1960. Advances in recent years include knowledge of the long-term fate of colon [169, 170] and jejunal interpositions [171], gastric tube [172, 173] and total gastric replacements [174], the importance of an isoperistaltic segment [175], and the increased usage of free intestine autotransplants for segmental replacement, particularly of the cervical esophagus [176, 177].

Other Advances

A number of additional technical and scientific advances have been made in specific fields. To the extent that this list is not conclusive, my apologies are offered to those offended.

In pediatric thoracic surgery advances in anesthesia and neonatal intensive care allow correction with diminished mortality for many of the congenital chest, pulmonary, and esophageal abnormalities within the limits of the disease. Tracheoesophageal fistula is now recognized as a condition that can be treated by delayed intestinal interposition in infants in whom primary repair cannot be safely achieved. Unless other anomalies are present, the survival rate from this anomaly should be greater than 90%, a remarkable improvement from 25 years ago [178, 179]. Techniques for correction of pectus excavatum are well established in several large series, and indications for correction of the more severe versions of this anomaly are generally accepted for physiological as well as cosmetic reasons [180–182]. Congenital diaphragmatic hernia remains a problem because of the insufficient lung development [183]. In utero fetal experimental operations offer promises for new understanding of this condition [184, 185].

The role of thymectomy for myasthenia gravis seems well established [186], but technical controversies continue as to the transcervical [187] versus transsternal approach [188] for the procedure. Extending thymectomy to the treatment of red cell aplasia is a recent development [189]. Management of some conditions is simplified by the use of specific surgical approaches such as the transaxillary approach to pleurectomy, which avoids the discomfort and scar of a major thoracotomy [190], and the subxiphoid approach to establish a pericardial window for uremic and other types of pericarditis [191]. The axillary approach to first rib resection is well accepted and widely practiced [192], but controversy continues about the specific indications for the procedure [193–195].

Transthoracic vertebral surgery in conjunction with pediatric orthopedic surgery for scoliosis and with neurosurgery for the dumbbell neurogenic tumors is now standard practice [196].

Diaphragmatic pacing is successfully employed for chronic respiratory insufficiency and apnea of central nervous system origin [197].

The pleuroperitoneal shunt greatly simplifies the management of chylothorax [198] and is under evaluation for treating persisting pleural effusions of other origins [199]. It is employed in malignant pleural effusions with less certain results due to clogging of the shunt in some cases.

The importance of myotomy in treating epiphrenic [200] and Zenker's diverticulum [201] is well established. The elimination of the need to perform a diverticulectomy greatly simplifies and increases the safety of surgical treatment.

The extension of the esophageal myotomy in patients with vigorous achalasia reduces the problem of recurring esophageal spasm postoperatively [65], and the routine application of a modified antireflux repair after myotomy for achalasia nearly eliminates failures caused by reflux esophagitis with stricture or inadequate myotomy [201].

The nature of the Schatzki ring as being the mucosal gastroesophageal junction and not necessarily related to gastroesophageal reflux has been clarified [202, 203]. Its treatment by dilation is now generally accepted.

Mortality and morbidity from esophageal rupture remain high, but a number of newer techniques can be employed in specific instances [204–207]. The role for nonoperative treatment of esophageal perforations localized and freely draining back into the lumen of the esophagus is now generally accepted [208, 209].

The improvement and refinement of stapling techniques [210–212] and availability of synthetic suture material of various types has improved steadily during the past quarter century and contributes to the efficiency of surgical procedures and to achieving standardized methods for anastomotic techniques. The stapling methods are widely used in esophageal and pulmonary surgery but continue to have an incidence of both leakage and stricture rates when applied to the esophagus comparable with or greater than those achieved by handsewn anastomoses.

The risk of thromboembolism and serious pulmonary embolus is substantially reduced by the adoption of prophylactic anticoagulant regimens for major operations [213]. The development of vena cava filters, particularly the Greenfield filter, in recent years simplifies the problem of thrombosis and recurrent pulmonary embolism [214, 215]. Suction techniques for retrieving the pulmonary embolus are successful in some cases [216].

From plastic and reconstructive surgery, techniques for major flap reconstruction are applied advantageously to problems in thoracic surgery [217].

The evolution of extensive esophagogastric devascularization reintroduces the thoracic surgeon to the management of bleeding esophageal varices [218, 219]. With continued disappointment in the long-term outcome of shunt operations both from recurrent bleeding and encephalopathy, more widespread use of extensive devascularization is taking place in some parts of the world and will probably increase in popularity in North America in the years ahead.

The use of intraluminal stents for caustic injury shows promise [220, 221]. The major problem is the appropriate selection of patients. Recognition that some of the newer drugs or inappropriate ingestion of chemicals such as Clinitest tablets can cause esophageal strictures leads to increased caution in diagnosing the cause of strictures [222]. Not all are caused by gastroesophageal reflux or lye ingestion [223].

Problem Areas That Remain Opportunities

In the past 25 years some methods have been investigated in human trials that have not yet proven effective. These should be viewed as first steps toward future advances rather than failures not to be investigated further.

The role of the surgeon in the medical pulmonary diseases remains unclear and somewhat frustrating. Early hopes for glomectomy in the treatment of asthma have not worked out [224]. Enthusiasm 25 years ago for the tailoring of emphysematous blebs is diminished substantially [225]. Diffuse interstitial disease still eludes effective treatment unless lung transplantation proves to be a solution. Aggressive efforts at extrapleural pneumonectomy for mesothelioma are generally not rewarding [226]. Initial promise of intrapleural Calmette-Guérin bacillus to improve the results of resection for lung cancer is not proven [227], but more sophisticated applications of immunological enhancement such as interleukin-2 for lung and esophageal cancer patients loom on the horizon. Efforts at controlling postthoracotomy pain by electrical stimulation [228], freezing of intercostal nerves [229], or long-lasting nerve blocks [230] are not a panacea. However the numbers of patients suffering from crippling postthoracotomy neuralgias appears diminished with attention to less traumatic techniques, in particular not removing the rib at the time of thoracotomy.

The aortoesophageal fistula as a complication of neoplasm or operation remains largely an unsolved technical challenge [231, 232]. Efforts to resect and replace the aorta in continuity with an invading pulmonary or esophageal carcinoma have not proven rewarding. Extending the

Table 1. Areas Included in Residency Leading to Certification in Surgery and Thoracic Surgery, Massachusetts General Hospital, 1964

Cardiothoracic[a]
Gynecology[a]
Plastic[a]
Colorectal[a]
Fractures[a]
Emergency[a]
Vascular[b]
Pediatric[b]
Critical care[b]
Oncology[c]
Transplantation[c]
Burns[c]
Gastrointestinal/pancreatobiliary[c]
Endoscopy[c]
Hand[c]
Head and neck[c]
Endocrine[c]
Trauma[c]

[a] This area now has an independent board. [b] This area now has a special certificate. [c] This area now has special fellowships.

resection for large tumors is still unproven and on doubtful theoretical grounds.

Intubation of the esophagus for palliation remains of interest for the many inoperable cases and can now be done endoscopically, but no single method of intubation is yet trouble-free [233, 234]. Connecting an esophageal stoma to a gastrostomy by an extracorporeal tube connection is occasionally useful but is not well developed technologically [235].

The initial promise of calcium channel blocking drugs for esophageal motor disorders is not realized, and the management of diffuse esophageal spasm, particularly when causing pain, remains a major dilemma for the esophageal surgeon and gastroenterologist [65].

Evolution of Thoracic Surgery Education

All of the aforementioned advances coupled with the incredible growth in cardiac surgery add greatly to the knowledge required of the thoracic surgeon. This leads appropriately to more formal structuring of the educational programs in the specialty. For some years discussion has centered around the merits of separating general thoracic surgery from cardiovascular surgery. In considering the advances of the past 25 years it is interesting to note how many of them are derived from innovations in other specialties and applicable to patients with thoracic disease. Comparing current residency programs with those of a quarter century ago, the difference in exposure to other disciplines is striking. Table 1 indicates the contents of the chief residency experience at the Massachusetts General Hospital at the time this Society was founded and how much of that experience is now being separated and unavailable to the physician in training to become a thoracic surgeon.

While we acknowledge the increasing amount of knowledge and skill required to be a cardiothoracic surgeon today, and attempt to lengthen the residency programs, we must also remain aware that many of the advances in the past and undoubtedly in the future in our field will come from exposure to ideas being developed on other forefronts of surgery and medicine. In efforts to improve the education and immediate results of today's practice of thoracic surgery, we must not become so isolated as to foreclose our future. We are already at great risk of doing so by abandoning areas of our specialty such as endoscopy, critical care, diaphragmatic and upper abdominal problems, chest wall reconstructions, and other aspects of general thoracic surgery that were very much a part of our specialty a quarter century ago but are becoming increasingly less so as we enter the 1990s.

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Technical and Scientific Advances in Cardiac Surgery Over the Past 25 Years

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President Lindesmith, Colleagues: More than you can possibly know, I feel honored and proud to have been invited to speak during the celebration of the 25th birthday of The Society of Thoracic Surgeons.

The advances in cardiac surgery over the past 25 years are inextricably bound with ideas and events preceding 1964 (Table 1). In fact, in my opinion, the technical and scientific advances in cardiac surgery really began with the ending of World War II. The surgical treatment of chronic constrictive pericarditis had already been developed by Rehn, Sauerbruch, Churchill, Beck, and others; the surgical closure of a patent ductus arteriosus had been accomplished by Gross; and during the war itself, Craaford in Sweden and Gross in Boston had probably independently accomplished the repair of coarctation. John Gibbon had already published, in 1939, his landmark report on maintenance of life with a nonbiological, so-called mechanical pump-oxygenator.

It is, however, impossible, on looking back 50 years, to comprehend the enormity of the energy that was released by the ending of World War II in 1945. Dr Gibbon returned from naval duty in the South Pacific to resume his work with pump-oxygenators and cardiopulmonary bypass. Bigelow returned from the European theater of operations to continue his basic investigations leading to cardiac surgical procedures during profoundly hypothermic total circulatory arrest. Lillehei returned from the North African theater of operations to the stimulating environment of the University of Minnesota. And a similar transition was being experienced by many of us. Industry began making great profits, and money became available. The United States government was literally anxious to spend its dollars in support of research. Some time was required, of course, for the redirection of these enormous energies of war to peacetime endeavors and for these endeavors to mature and grow, and that explains the delayed growth in scientific publications about cardiac surgery in *The Journal of Thoracic and Cardiovascular Surgery* that is evident in Figure 1. But some measure of the energy involved is plainly evident.

Support Systems

Cardiopulmonary bypass through a pump-oxygenator is surely the basic support system for cardiac surgery. Ivan Brown, working with Sealy, Young, and others at Duke University Medical Center in the middle and late 1950s, first combined cardiopulmonary bypass with another important modality, hypothermia, and for this, Brown and the Harrison Radiator Division of General Motors combined forces to develop the Brown-Harrison heat exchanger (Fig 2).

Brown's contributions and the development of membrane oxygenators more than 10 years ago may be the last fundamental advances that have been made in pump-oxygenators to date. Venous return is still activated by the effect of gravity in nearly all systems used for patients, and a venous reservoir is necessary. This imposes the need for the pump-oxygenator system to be close to the floor and, by this necessity, far away from the patient, and the venous reservoir demands a considerable blood volume and negates serious efforts to reduce priming volume in an important way. DeBakey-type pumps send arterialized blood back to the patient in most systems. True, contemporary pump-oxygenators have alarm systems, on-line monitoring, computer readouts, and a price that is about four times that of the infinitely more complex BMW 535i. Interestingly, nearly all these so-called modern characteristics, including costs, were possessed by the Mayo-Gibbon pump-oxygenator (Fig 3) with which my colleagues and I began the first series of open heart operations with a nonbiological pump-oxygenator in 1955.

It is possible to use a rather different system that is simpler and easier to run and has an inherently small priming volume (Fig 4). We have used this exact system in the animal research laboratory for 2½ years. The pump head, oxygenator, and heat exchanger are at the subject's left shoulder, even more so than could be shown in the figure, while the controlling console is 122 cm (4 ft) removed. This means that the blood pathway through tubing is very short. No venous reservoir is in the system; rather, the Bio-Medicus pump sucks blood directly from the patient's venous system and pumps it back through a

Table 1. Technical and Scientific Advances in Cardiac Surgery

The support systems
The hospital environment
The surgical procedures
Myocardial management
The developing science of comparing and predicting

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

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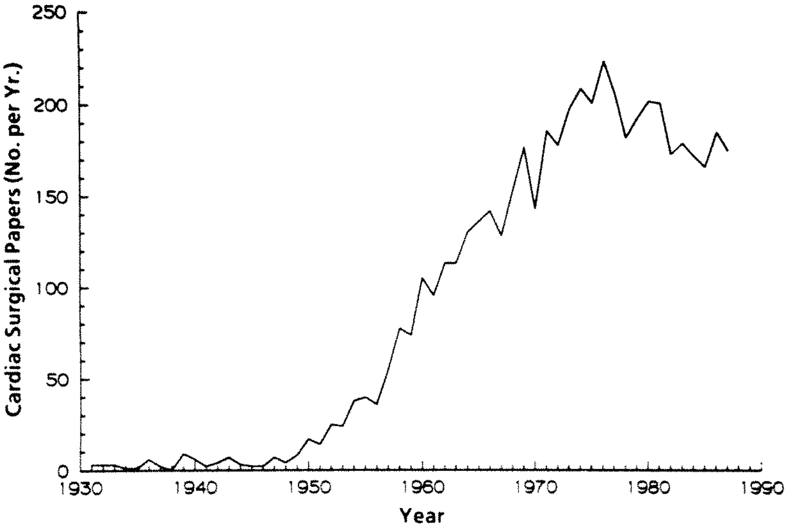
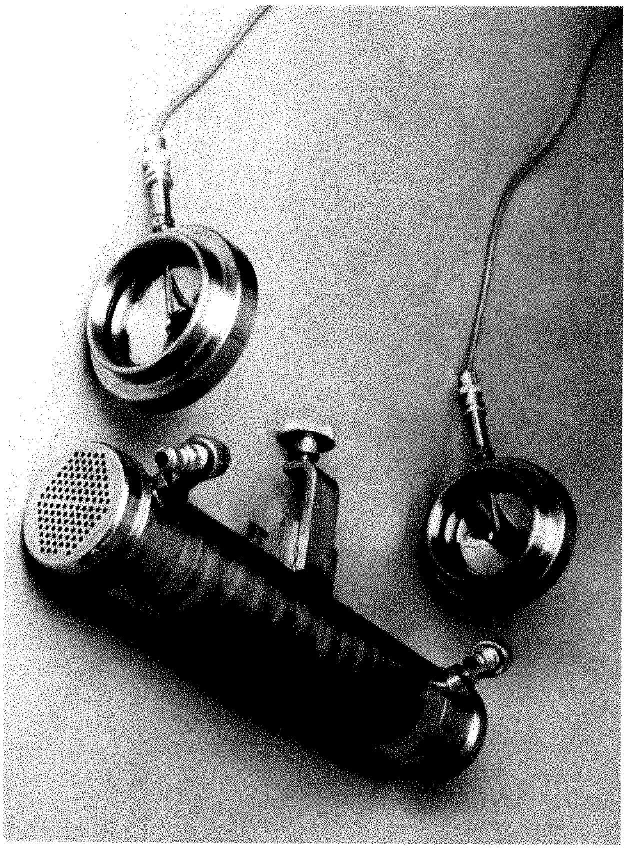


Fig 1. The number of cardiac surgical reports (n = 8,981) published in The Journal of Thoracic and Cardiovascular Surgery *between 1931 and 1988 by year of publication.*

membrane oxygenator and a heat exchanger. A "filler bag" is alongside but not part of the flow circuit, and is used for storing some of the patient's blood volume during perfusion if necessary and for storing the fluid that may be added to the flow circuit. Because of the inherent characteristics of the Bio-Medicus pump and certain added controls, the system has a high degree of safety. Note the priming volume of 250 mL for a flow that is adequate for neonates and infants up to about 2 years of age, rising to about 750 mL for adults. Bio-Medicus is far along in the development of this type of system for clinical use.

Brown IW Jr, Smith WW, Emmons WO. An efficient blood heat exchanger for use with extracorporeal circulation. Surgery 1958;44:372–7.



Sealy WC, Brown IW, Young WG. A report on the use of both extracorporeal circulation and hypothermia for open heart surgery. Ann Surg 1958;147:603–13.

Fig 2. Mayo version of the Brown-Harrison heat exchanger developed by Brown and his colleagues at Duke University, and the publications related to it.

Probably, a normal man could be placed on cardiopulmonary bypass for 120 minutes with a very low chance of death and little morbidity (Table 2). I estimate that a normal individual would have about a 0.5% chance of having important pulmonary dysfunction after this period of cardiopulmonary bypass. On the other hand, a patient undergoing repair of tetralogy of Fallot with pulmonary atresia may have a 10% chance (20 times greater) of having important pulmonary dysfunction and a patient with chronic obstructive lung disease undergoing coronary artery bypass grafting, a 20% chance, which is 40 times that of a normal subject.

The damaging effects are certainly less, although not absent, with shorter periods of cardiopulmonary bypass, but there are limitations to that approach (Table 3). For example, all of us working during the first few years of intracardiac surgery repaired ventricular septal defects within ten to 20 minutes of cardiopulmonary bypass and tetralogy of Fallot, within 30 to 40 minutes. As the experience with cardiopulmonary bypass grew and improvements were made, every surgeon began to use the longer time available to do better and more complex operations. Further, the patients now tend to be sicker, and smaller or older, and the operations tend to be still more complex and time consuming. Were we to succeed in some of the molecular and immunological investigations that are envisioned, we could prevent most of the damaging effects of cardiopulmonary bypass, and improve considerably the results of cardiac surgery. Already this line of investigation has, by serendipity, led to the discovery that aprotinin (Trasylol) dramatically reduces bleeding after cardiopulmonary bypass, although the

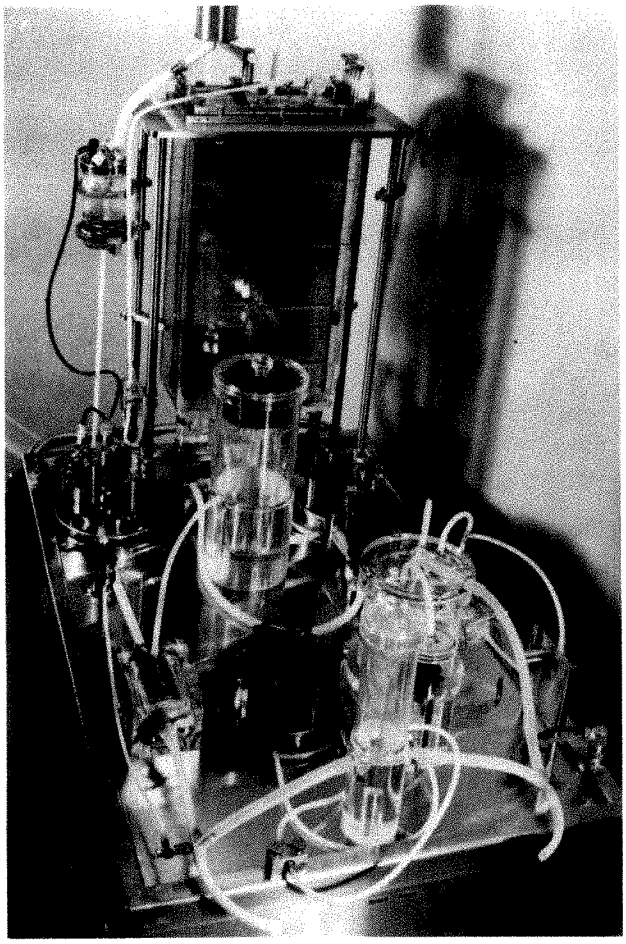


Fig 3. Mayo-Gibbon pump-oxygenator, as it was used in 1955 during the first series of open heart operations accomplished with the aid of a nonbiological pump-oxygenator.

mechanisms of action of this drug are not yet fully understood.

Hospital Environment

No doubt, the first intensive care units were cardiac surgery intensive care units. The very first one may have been on the fifth floor of St. Mary's Hospital, a part of the Mayo Clinic complex in Rochester, MN, where in late 1956 we established a cardiac surgery intensive care unit. Intensive care units are now commonplace, but in my judgment, these, too, in most hospitals, have failed to take full advantage of the technological advances that could make them safer for patients and less labor intensive for nurses. Be that as it may, the cardiovascular surgery intensive care unit and the modern cardiac operating room are both a result and a cause of the development of cardiac surgery over the last 40 years.

Surgical Procedures

Table 2. Manifestations (at Least in Part) of the Damaging Effects of Cardiopulmonary Bypass

Bleeding
Generalized edema
Cardiac and pulmonary dysfunction
Cerebral dysfunction
Acute hypermetabolism
Delayed febrile state
Others

The fabulous array of cardiac surgical procedures available today is the result of an unbelievably exciting and dynamic era in cardiac surgery extending for about 20 years after 1954 and 1955, certainly a most interesting and exciting part of my professional life. Lillehei began successfully closing ventricular septal defects in 1954, and he and we soon began developing methods, including transannular patches, to overcome the right ventricular outflow tract obstruction of tetralogy of Fallot. New and successful operations were being described almost daily for heretofore uncorrectable forms of congenital heart disease, and sometimes we, the surgeons, had to describe the anomalies themselves for the first time. Valvar surgery quickly developed. Lillehei and, independently, Merendino began successfully to repair incompetent mitral valves in 1957. A few years later in 1960, McGoon and colleagues began repairing mitral incompetence from ruptured chordae of the posterior leaflet with outstanding success. Earle Kay developed an entirely circular annuloplasty just a few years later, clearly the forerunner of the highly effective and refined Carpentier mitral annuloplasty ring. In 1961, Albert Starr not only invented, with Edwards, one of the first prosthetic heart valves for human use but also popularized the first prosthetic valve replacement.

Donald Ross in London and Barratt-Boyes in New Zealand, borrowing from the earlier clandestine work of Gordon Murray in Toronto, introduced in the early 1960s the use of aortic valve allografts both for aortic valve replacement and valved extracardiac conduits. Soon Mark O'Brien in Brisbane, Australia, introduced cryopreservation of these allografts. Chronic thoracic aortic aneurysms and acute aortic dissections came under successful surgical treatment, largely the result of the brilliant work of DeBakey, Cooley, Morris, Crawford, and their colleagues. First poudrage, then the internal mammary artery implant, and then coronary artery bypass grafting appeared

Table 3. Hypothesis: The Damaging Effects of Cardiopulmonary Bypass Are Mediated by a Whole Body Inflammatory Reaction, With Activation of These Elements

Complement cascade
Kallikrein cascade
Coagulation cascade
Fibrinolytic cascade
Arachidonic acid cascade
Leukocytes
Platelets
Catecholamine response

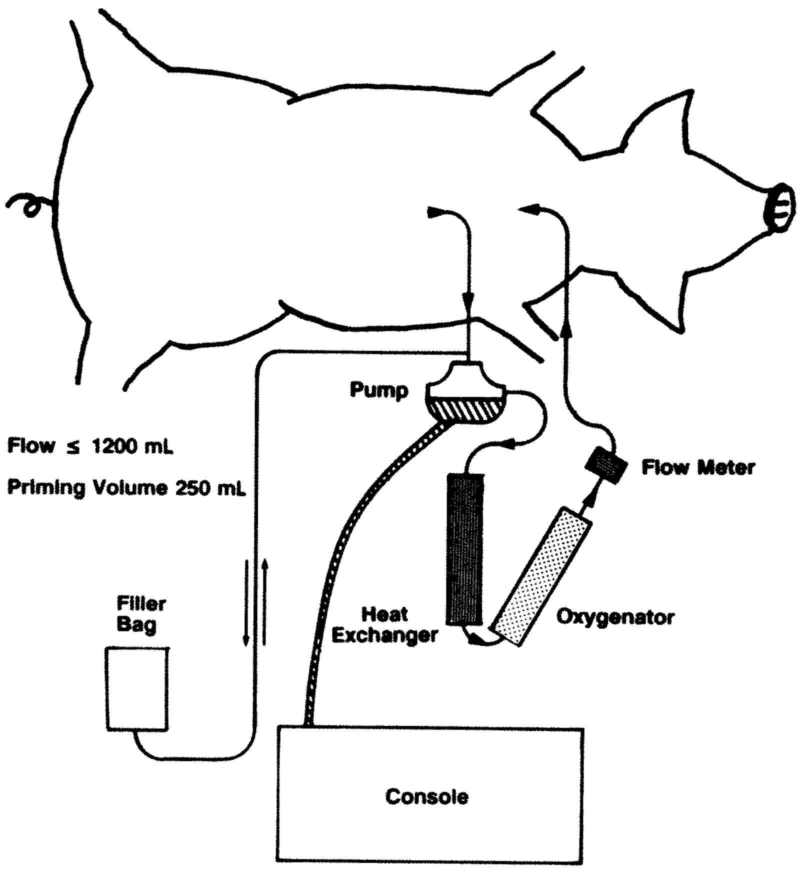
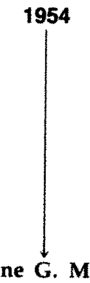


Fig 4. Pump-oxygenator system developed at The University of Alabama at Birmingham.

and revolutionized the treatment of ischemic heart disease.

I hope you can sense that in that period, almost each day brought an exciting advance, the value of which was self-evident. Publications in that early era could be simple records of achievement, and there was no need for *p* values, no need to predict and compare. I am grateful that I had the opportunity of being a participant in it. I hope, by the way, that you can also sense that all of what seems new today may not be so new after all.



Taber RE, Morales AR, Fine G. Myocardial necrosis and the postoperative low-cardiac-output syndrome. Ann Thorac Surg 1967;4:12–28.

Najafi H, Henson D, Dye WS, Javid H, Hunter JA, Callaghan R, Eisenstein R, Julian OC. Left ventricular hemorrhagic necrosis. Ann Thorac Surg 1969;7:550–61.

Fig 5. The interval between the first open heart operations and the recognition that damage to the heart itself during an operation was an important contributor to death early postoperatively.

Myocardial Management

During the first 13 years of the exposure of the world to cardiac surgery, not a word was said about the possibility that many of the deaths after cardiac operations were due to damage to the heart itself. Then *The Annals of Thoracic Surgery* published two reports that served as a paradigm (Fig 5). Soon coronary artery bypass grafting appeared, and myocardial necrosis as a complication of cardiac operations was again documented. Most people inferred that the infarction was primarily related to the coronary artery disease, but this was wrong. In 1973, Hultgren and colleagues showed again, as had Taber and co-workers and Najafi and colleagues earlier, that typical localized myocardial infarction, as well as more diffuse subendocardial necrosis, could occur after a cardiac operation in the complete absence of coronary artery disease.

Thus the highly important concept of myocardial management has developed (Table 4), and an enormous number of studies concerning this area have been published. And yet many of the laboratory and clinical data are conflicting, and there are unresolved paradoxes.

Table 4. Factors Involved in Myocardial Management

Myocardial temperature
Cardioplegia
Reperfusion

Table 5. Combined Aortic and Mitral Valve Replacement[a]

Method of Myocardial Management	No. of Operations	Hospital Deaths No.	Hospital Deaths %	Hospital Deaths CL
Two periods of cold ischemic arrest	18	1	5.6	0.7%–17.6%[b]
Cold cardioplegia	211	18	8.5	6.5%–11.0%[b]
Single period of cold ischemic arrest	109	10	9.2	6.3%–13.0%[b]
Coronary perfusion, 32°C	274	40	14.6	12.4%–17.1%
Mixed methods	17	5	29.4	17.0%–44.8%
Total	629	74	12	10%–13%

[a] These double-valve replacement operations were performed between 1967 and 1981 at the University of Alabama at Birmingham. [b] $p = 0.87$ by χ^2 test for these three methods.

CL = confidence limits.

Table 6. Primary Combined Aortic and Mitral Valve Replacement[a]

Incremental Risk Factors for Death[b]	Hazard Phase Early	Hazard Phase Constant
Demographic		
Age (yr) (older)	No	Yes
Body surface area (m^2) (larger)	Yes	No
Clinical and hemodynamic status		
NYHA class (I–V) (higher)	Yes	Yes
Pulmonary vascular resistance (units/m^2) (higher)	No	Yes
Morphological		
Important aortic and mitral regurgitation	Yes	No
Left ventricular enlargement (1–6) (greater)	No	Yes
Ischemic heart disease requiring CABG	No	Yes
Surgical		
Nonuse of cardioplegia	Yes	No
Global myocardial ischemia time (min) (longer)	Yes	No

[a] There were 569 patients who underwent primary double-valve replacement at the University of Alabama at Birmingham between 1967 and 1981. [b] This is a partial list.

CABG = coronary artery bypass grafting; NYHA = New York Heart Association.

Here is an example. We performed 629 double-valve replacement operations between 1967 and 1981, a 14-year period in which various methods of myocardial management were in use (Table 5). Surely there is no evidence from this simple analysis of the clinical experience that cardioplegia was better than simple profoundly hypothermic ischemia. Table 6 is the result of a multivariate risk-factor analysis in the hazard function domain of the 569 patients who underwent primary double-valve replacement. The early phase of risk includes the first several postoperative months. We see here that nonuse of cold cardioplegia is a risk factor for death in the early period after operation. Now, which do you believe, the simple straightforward analysis or the more complex multivariate analysis? Or do you believe neither, and rely on the results of isolated rat heart studies or studies in dogs or pigs? Suddenly we have left the exciting earlier era when simple records of achievement sufficed for our publications, and have come into an era where things are more difficult and more complex, and the old simple

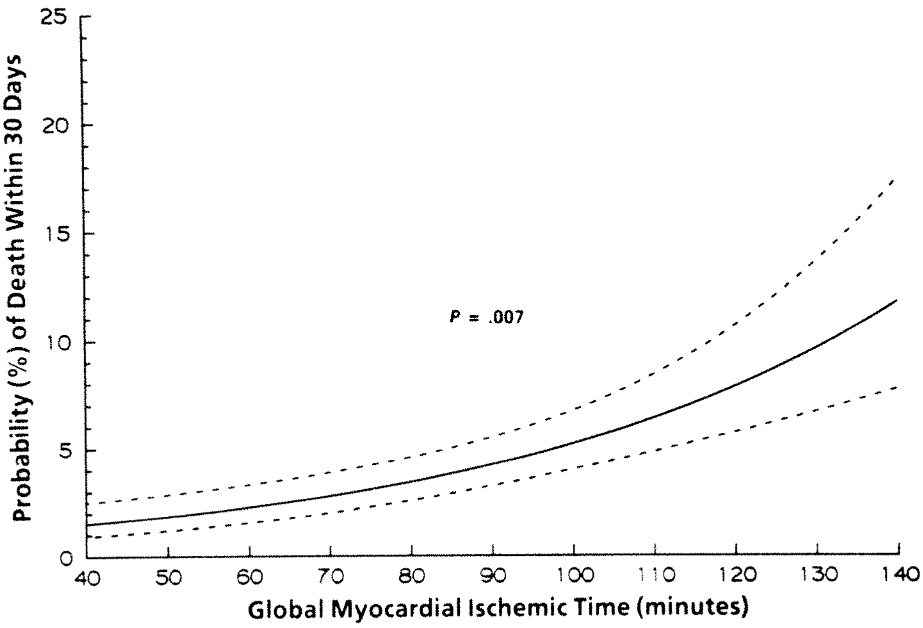


Fig 6. A solution to the multivariate risk-factor equation for death after primary simultaneous aortic and mitral valve replacement with or without concomitant tricuspid valve operation and coronary artery bypass grafting. This shows the relationship between time of global myocardial ischemia during cold cardioplegia and the probability of death within 30 days after operation. Data are from The University of Alabama at Birmingham, and represent results in 569 patients operated on between 1967 and 1981. The broken lines *enclose the 70% confidence intervals. (Details of the analyses and the multivariate risk-factor equation are available from me.)*

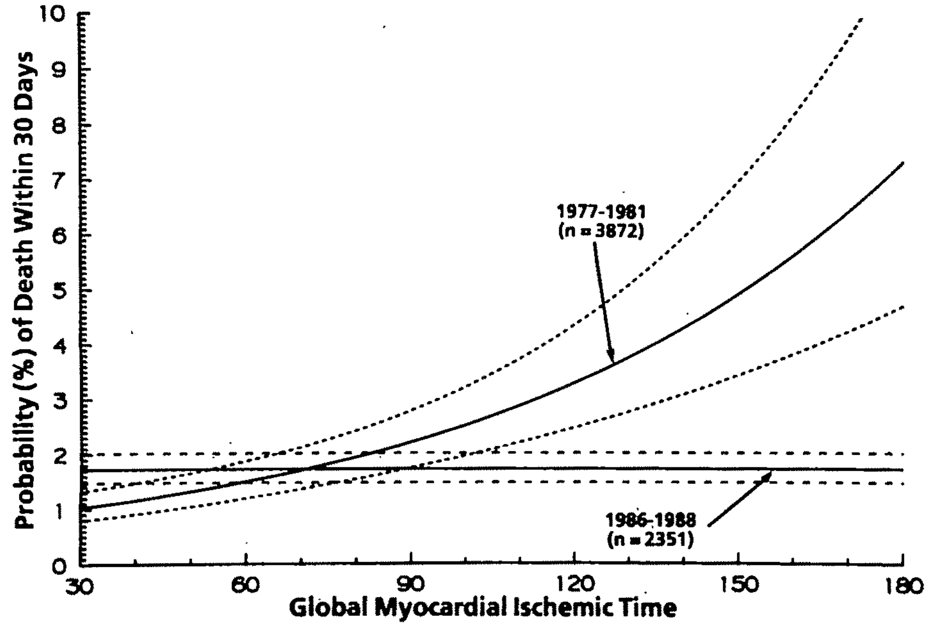


Fig 7. Multivariate risk-factor analyses of The University of Alabama at Birmingham experience with primary isolated coronary artery bypass grafting. The nomograms relate the time of global myocardial ischemia to the probability of death within 30 days after operation. The broken lines enclose the 70% confidence intervals. (Details of the analyses and the multivariate risk-factor equation are available from me.)

methods of study do not suffice. Even our traditional reliance on animal studies is beginning to fail us in the area of myocardial management, because our animal models vary so much from one to another and from humans that inferences concerning people can be drawn from such models only with great caution.

The Developing Science of Comparing and Predicting

In my judgment, one of the advances that has not been made in cardiac surgery is the widespread development of the capability of using clinical experiences in a reasonably rigorous way to derive clinically important inferences. And we now need this. As exciting as were the early days, that excitement has been dying over the last 10 years, perhaps in part, as my son Jim tells me nearly daily, because "things are much tougher than they used to be." In any event, in most areas of cardiac surgery a plateau has developed. Why has not the science of cardiac surgery been better developed to move things upward to a new plateau? The reasons are numerous, in my opinion, but one of them is that many cardiac surgeons have a deep suspicion of any complexity in experiments, data, or methods of analysis, and this has led to a failure to use modern methods of research and analysis that, paradoxically, would result in simpler and more valid inferences.

The nomogram of a solution to the multivariate equation I mentioned a moment ago shows the increasing probability of death within 30 days after double-valve replacement as the time of global myocardial ischemia during cardioplegia lengthens (Fig 6). Other nomograms from primary isolated coronary artery bypass grafting illustrate the effect of myocardial management on death early after the operation (Fig 7). One curve is the solution of a multivariate equation of the 1977–1981 experience at The University of Alabama at Birmingham, and shows a rising probability of death with longer times of global myocardial ischemia, just as in the double-valve replacement experience. The other curve is from the 1986–1987 experience with coronary artery bypass grafting at the same institution. It shows that in the more current experience, there was *no* incremental risk from longer aortic cross-clamp times. The difference in the two experiences is that in 1986 and 1987, in most of the patients with long cross-clamp times, myocardial management included controlled and initially hyperkalemic reperfusion with otherwise unmodified blood.

Laboratory experiments have been and will continue to be critically important in the development of the science of myocardial management. However, for the answers to be correct and clinically applicable in this and many other aspects of cardiac surgery, the same effort and the same rigorous and scientific methods must be applied to *clinical* data. We are now in an era in which, in my opinion, we must not only continue to make technical and scientific advances, but for many, many reasons must also document their importance by detailed data collection and the use of proper analyses for comparing and predicting.

Conclusion

Well, President Lindesmith, thank you for the privilege of reviewing in a small and incomplete way, the exciting times in which we have lived and in which The Society of Thoracic Surgeons has developed.

Platelet and Neutrophil Activation in Cardiopulmonary Bypass

Robert W. Colman, MD

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My colleagues and I have employed a simulated extracorporeal circuit to help define blood cell changes during clinical cardiopulmonary bypass. Platelet count decreases sharply due to temporary adhesion to the circuit. Platelets degranulate, synthesize and release thromboxane A_2, and lose the ability to aggregate with adenosine diphosphate and epinephrine. These changes are also due to the loss of α_2-adrenergic and fibrinogen receptors. The neutrophil count decreases to a lesser extent, but neutrophils also are stimulated to secrete lactoferrin and elastase concomitant with activation of plasma kallikrein. Although lidocaine can inhibit the neutrophil activation and prostacyclin can inhibit the platelet stimulation, prostaglandin E_1 appears to prevent both neutrophil and platelet alterations.

(Ann Thorac Surg 1990;49:32–4)

Clinical cardiopulmonary bypass (CCB) is required by over 200,000 Americans each year. Unfortunately, a truly biocompatible material does not exist and efficiency of gas transport requires a hemodynamic design that promotes blood cell injury. Routine CCB results in red cell hemolysis, prolonged bleeding time due to platelet injury [1], and activation of neutrophils [2]. Although the clinical manifestations of cellular injury are typically mild in CCB of one to three hours, during longer bypass excessive blood loss and endothelial damage by sequestered leukocytes [3] may result. Moreover, these changes may preclude implementation of long-term circulatory assist devices. Thus, it is of obvious importance to understand the mechanisms of platelet and neutrophil alteration in CCB in order to develop strategies to prevent or minimize these changes. Unfortunately, this is not easy to accomplish in CCB, where the entire cardiac output passes through multiple components of the perfusion system and the procedure is technically complex and varies from patient to patient. Moreover, the blood is diluted, filtered, washed, and cooled and the patient receives drugs, anesthesia, and sometimes transfusions.

Therefore, to better define the interaction between the plasma, blood cells, and artificial surfaces, for the past 12 years my colleagues and I have been using a simulated extracorporeal circulation (SECC) that employs heparinized human blood in a circuit containing an oxygenator [4]. Observations in this in vitro model have not only defined the changes in platelets and begun to elucidate mechanisms of neutrophil injury, but have begun to suggest useful pharmacological approaches to modifying cellular injury in CCB. This report reviews the events that characterize the behavior of platelets and neutrophils at the synthetic surface interface, describes cellular alteration accompanying cardiopulmonary bypass, and describes the pharmacological interventions that might mitigate adverse platelet and neutrophil surface interactions.

Platelet Alterations

By five minutes into CCB, platelet counts decline to 40% of prebypass level (Fig 1). When human blood anticoagulated with heparin at 37°C is recirculated in a standard silicone rubber circuit containing a membrane oxygenator—SECC—there is a decrease to 20% of initial values within two minutes with a slow increase over the next two hours [5]. This loss is clearly related to platelet adhesion to the circuit [4], although the formation of platelet aggregates may also contribute. Platelet loss is proportional to both flow rate and surface area of the circuit [6]. During CCB platelets secrete the contents of the α-granules as reflected by an increase in the plasma levels of β-thromboglobulin (Fig 1). In SECC platelets appear degranulated on electron microscopy [4]. Another indication that the surface activates platelets is that the synthesis of thromboxane A2 has been detected under these circumstances [7]. The resulting platelets show markedly reduced sensitivity to soluble aggregation agents such as adenosine diphosphate and epinephrine.

Although this hyporesponsiveness may be due in part to the degranulation with expected loss of the positive feedback effects of released adenosine diphosphate, serotonin, fibrinogen, and calcium, there are other reasons for the decreased function of platelets after recirculation. There is a 50% decrease in α_2-adrenergic receptors on the platelet surface at two minutes [8]. The decrease in these receptors responsible for epinephrine-induced platelet aggregation was correlated with a ninefold increase in the concentration of epinephrine required to induce platelet aggregation. At two hours a total lack of response to epinephrine was paralleled by a complete loss of α_2-adrenergic receptors as measured by binding of the competitive antagonist [^{3}H]yohimbine. Fibrinogen binding to

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Invited lecture sponsored by the Coordinating Committee for Continuing Education in Thoracic Surgery (CCCETS), presented at the Twenty-third Postgraduate Program of The Society of Thoracic Surgeons, Baltimore, MD, Sep 10, 1989.

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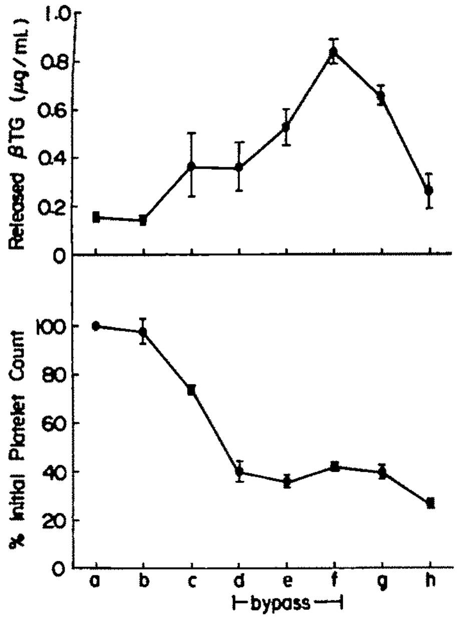

Fig 1. Platelet counts and plasma levels of platelet β-thromboglobulin (βTG) during clinical cardiopulmonary bypass (CCB). The percent initial platelet count and released βTG was determined (a) before induction of anesthesia; (b) after anesthesia, before heparin; (c) after heparin, before CCB; (d) five minutes after start of CCB; (e) 45 minutes after start of CCB; (f) just before CCB ended; (g) 60 minutes after CCB; (h) 24 hours after CCB. Each point represents the mean ± standard error of 4 patients.

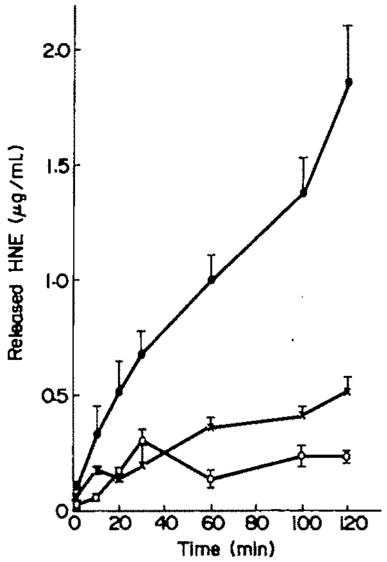

Fig 2. Plasma levels of human neutrophil elastase (HNE) in recirculated blood during simulated extracorporeal bypass. Released HNE is expressed as micrograms of HNE per milliliter of plasma. Values were obtained when heparin-anticoagulated blood was recirculated in the presence of prostaglandin E_1 (0.3 μM, X) or lidocaine (100 μM, O) or in the absence of additional drug (●). Each point represents the mean ± standard error of seven separate determinations.

platelets is the biochemical correlate of platelet aggregation. After two hours of recirculation, the number of fibrinogen binding sites exposed by adenosine diphosphate or chymotrypsin decreased twofold to threefold [9]. Similar results were found when levels of a monoclonal antibody binding to the fibrinogen receptor platelet glycoprotein IIb/IIIa complex were measured. These changes were correlated with the decrease in the maximal rate of platelet aggregation by fibrinogen. The mechanisms of the loss of receptors for both fibrinogen and epinephrine may be due to platelet adhesion to the circuit.

Neutrophil Alterations

We [10] demonstrated in an early study the release of the lysosomal enzymes N-acetyl-β-glucosaminide and acid phosphatase during SECC. However, the source was not clear because these enzymes could have arisen from both platelets and neutrophils. More recently, human neutrophil degranulation was definitively demonstrated in both SECC and CCB. We [2] measured two neutrophil proteins: lactoferrin, a specific granule marker, and human neutrophil elastase, an enzyme derived from azurophilic (lysosomal) granules. In CCB and SECC, neutrophil counts decline to 67% of control, but this decline is not nearly as great as that of the platelet count. Levels of both lactoferrin (not shown) and elastase (Fig 2) rise dramatically in SECC and to a lesser but significant extent in CCB (Fig 3). Unlike for platelets, for neutrophils we believe that soluble mediators rather than adhesion are responsible as neutrophils are rarely found adherent to the circuit

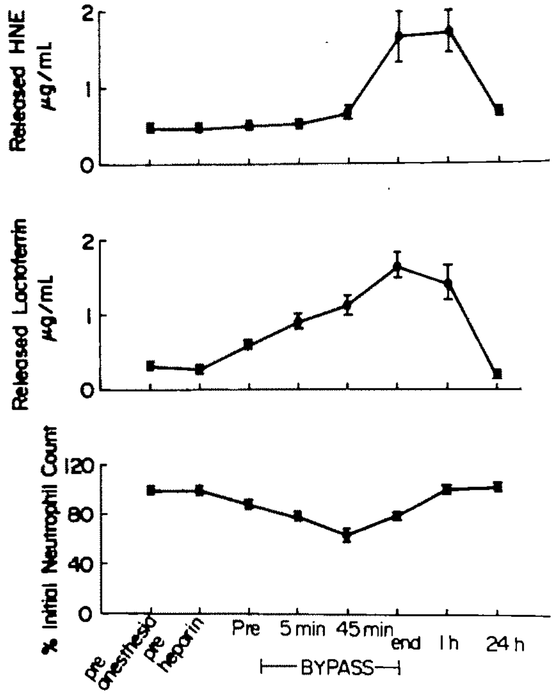

Fig 3. Neutrophil counts, plasma levels of neutrophil lactoferrin, and plasma levels of human neutrophil elastase (HNE) during clinical cardiopulmonary bypass (CCB). The percentage initial neutrophil count, released lactoferrin, and released HNE were determined before induction of anesthesia; after anesthesia, before heparin; after heparin, before CCB; five minutes after start of CCB; 45 minutes after start of CCB; just before CCB ended; 60 minutes after CCB; and 24 hours after CCB. Each point represents the mean ± standard error of 10 patients.

components. In recent studies [11] both kallikrein and the first component of complement were found to be activated, suggesting that kallikrein and C5a may play major roles in the degranulation of neutrophils.

Pharmacological Interventions

Despite the fact that platelets in extracorporeal circuits synthesize and release thromboxane A2, aspirin ingestion by donors is only partially successful in inhibiting platelet activation. Inhibitory prostaglandins (PGs) such as PGI_2 [12] and PGE_1 [5] are capable of maintaining the circulating platelet count and inhibiting granule release as monitored by β-thromboglobulin and electron microscopy. After the inhibitor is removed, the reactivity of platelets to agonists is preserved, as is the number of α_2 receptors [8] and fibrinogen receptors [9]. The bleeding time is normalized; however, the vasodepressor properties of these compounds limits their usefulness in humans.

Neutrophil degranulation is not inhibited by PGI_2 but is decreased by PGE_1 and even more effectively by lidocaine (Fig 2). Inhibitors of kallikrein or activated C1 may provide other approaches to preventing neutrophil activation.

My major scientific collaborators have been Dr L. Henry Edmunds, Jr, Dr Stefan Niewiarowski, Dr V. Paul Addonizio, and Yanina Wachtfogel. Without their contributions this work could not have been accomplished.

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Esophagectomy for Esophageal Disruption

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When esophageal disruption occurs in the presence of preexisting esophageal disease or is associated with sepsis or fluid and electrolyte imbalance, aggressive and definitive therapy often provides the only chance for patient salvage. Twenty-four adults (average age, 59 years) with intrathoracic esophageal perforations underwent esophagectomy: 15, transhiatal esophagectomy without thoracotomy; and 9, transthoracic esophagectomy. Restoration of alimentary continuity with an immediate cervical esophagogastric anastomosis was carried out in 13 patients. Eleven underwent a cervical or anterior thoracic esophagostomy, and 10 of them had a subsequent colonic (7) or gastric (3) interposition from 4 to 32 weeks (average time, 8.6 weeks) later. The perforations were due to esophageal instrumentation (9 patients), acute caustic ingestion (2), emesis (2), intrathoracic esophagogastric anastomotic disruption (2), and other causes (9). Preexisting esophageal disease in 20 patients included chronic strictures (10 patients), reflux esophagitis (3), esophageal cancer (3), achalasia (2), diffuse spasm (2), and monilial esophagitis (1 patient). Ten patients were operated on within 12 hours after the injury; 3, within 12 to 24 hours; and 11, within three to 45 days (average interval, 6.6 days). There were three hospital deaths (13%). Nineteen of the 21 survivors were able to swallow comfortably until the time of death or latest follow-up. Aggressive diagnosis and aggressive treatment of life-threatening esophageal perforations are advocated. Conservative procedures (repair, diversion, or drainage) for a perforation with preexisting esophageal disease often inflict more morbidity than esophageal resection, which eliminates the perforation, the source of sepsis, and the underlying esophageal disease. The decision to restore alimentary continuity in a single stage must be individualized.

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Few events encountered in the practice of thoracic surgery are associated with such devastating consequences as disruption of the intrathoracic esophagus, an event that carries a mortality rate nearly three times that of a cervical esophageal perforation [1]. Prolonged extravasation into the mediastinum of oral salivary digestive enzymes and bacteria as well as refluxed gastric acid, enzymes, and bile is nearly uniformly fatal without surgical intervention. The longer treatment is delayed, the greater the increase in mortality, to 40% to 66% after 24 hours or with established hydropneumothorax and mediastinal sepsis [2–4].

The dilemma confronting the thoracic surgeon is compounded by the variability of factors influencing the clinical setting: the duration of time between the occurrence of the leak and its diagnosis, the age of the patient, associated systemic illness, the hemodynamic stability of the patient, associated pleural contamination with empyema, and the presence of underlying intrinsic esophageal disease. No rigid set of guidelines applies to every patient with esophageal disruption, a successful outcome often depending on the surgeon's experience and ability to be flexible and innovative.

The desirability of preserving the esophagus when primary repair of the leak is tenuous has fostered a variety of alternatives for diversion in continuity or establishment of a controlled fistula. A protracted hospital course with the necessity for eventual reoperation is inherent in most of these procedures. More recently, improved results with esophageal replacement, particularly using the stomach as the conduit of choice [5–7], have influenced our approach to patients with intrathoracic esophageal disruption in the presence of preexisting esophageal disease or severe consequences of the mediastinal sepsis. This report reviews our experience with 24 patients with esophageal disruption treated by esophagectomy and either primary or delayed esophageal reconstruction.

Material and Methods

During the past 15 years, we have performed an esophagectomy in 24 patients with disruption of the intrathoracic esophagus, and a retrospective review of their clinical status influencing our choice of treatment, the operative approach, and the surgical outcome has been conducted. During the same period, an additional 27 patients with intrathoracic esophageal perforations were treated with either primary repair (22 patients) or drainage (5). Virtually all of these patients had little or no underlying intrinsic esophageal disease (eg, achalasia with minimal esophageal dilatation), and repair of endoscopic, early postemetic, or postoperative perforations diagnosed promptly was readily achieved. These patients are not analyzed in this report.

Among our 24 patients with perforations treated by esophagectomy were 12 male and 12 female patients ranging in age from 27 to 88 years (average age, 59 years). The oldest patients were 78, 79, 86, and 88 years of age (Tables 1, 2). The causes of the esophageal disruptions

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Table 1. Esophagectomy for Esophageal Disruption: Single-Stage Resection and Reconstruction

Patient No.	Age (yr)	Sex	Cause of Disruption	Intrinsic Esophageal Disease	Interval From Leak to Esophagectomy	Operation	Complications	Hospitalization After Esophagectomy (days)
1	69	M	Emesis	Reflux stricture	<12 h	THE/CEG	Continued sepsis, death 3 wk postop	. . .
2	86	F	Barrett's ulcer	Reflux stricture	20 days	THE/CEG	Respiratory insufficiency, sudden death 9 days postop	. . .
3	31	M	Endoscopy	Monilial esophagitis	7 days	THE/CEG	Anastomotic leak, sepsis, death 2 mo postop	. . .
4	65	F	Maloney dilation	Scleroderma-related reflux stricture	<12 h	THE/CEG	Aspiration, respiratory insufficiency	120
5	60	F	Balloon dilation	Megaesophagus achalasia	<6 h	THE/CEG	None	12
6	78	F	Maloney dilation	Reflux stricture	<4 h	THE/CEG	None	15
7	88	M	Maloney dilation	Reflux stricture	<4 h	THE/CEG	None	15
8	79	F	Maloney dilation	Reflux stricture	72 h	THE/CEG	None	10
9	69	F	Balloon dilation	Spasm, pulsion diverticulum	<6 h	THE/CEG	None	10
10	69	F	Emesis	Reflux stricture	14 days	THE/CEG	None	12
11	65	M	Maloney dilation	Reflux stricture, cancer	6 h	THE/CEG	None	12
12	59	F	Swallowed dental prosthesis	None	18 h	TTE/CEG	None	10
13	41	F	Takedown of Thal fundoplasty	Achalasia	8 h	TTE/CEG	None	14

CEG = cervical esophagogastrostomy; THE = transhiatal esophagectomy without thoracotomy; TTE = transthoracic esophagectomy.

were diverse: instrumentation in 9 (Maloney dilation, 6; balloon dilation, 2; and esophagoscopy, 1); emesis in 2; acute caustic ingestion in 2; intrathoracic esophagogastric anastomotic disruption in 2; reoperation on the esophagus in 3 (repair of recurrent hiatal hernia, 1; takedown of Thal cardioplasty, 1; and resection of recurrent pulsion diverticulum, 1); disruption of excluded esophagus in 2; and swallowed dental prosthesis, penetrating Barrett's ulcer, vagotomy, and spontaneous rupture (1 each). Preexisting esophageal disease was present in 20 of the 24 patients and included chronic strictures in 10 (nine due to gastroesophageal reflux and one due to caustic ingestion), achalasia in 2, reflux esophagitis in 3, carcinoma in 3 (1 also had a chronic reflux stricture), diffuse esophageal spasm in 2, and monilial esophagitis in 1.

The interval between the diagnosis of esophageal disruption and esophagectomy ranged from less than four hours to 45 days and averaged 6.6 days. Four patients were operated on within six hours after the injury, 6 from six to 12 hours, 3 from 12 to 24 hours, and 11 (46%) from three to 45 days (average time for this group, 15 days). The decision for esophagectomy rather than repair or drainage of the perforation was based on the presence of one or more factors adversely influencing the likelihood of success with either of the latter two approaches: distal obstruction (peptic stricture, tumor, or neuromotor dysfunction), other intrinsic esophageal disease (reflux or monilial esophagitis), severe local mediastinal contamination and inflammatory reaction, or established sepsis or fluid and electrolyte imbalance due to a previous unsuccessful attempt at closure or drainage.

Of the 24 patients, 15 (63%) underwent a transhiatal esophagectomy without thoracotomy and 9, a transthoracic esophagectomy, the decision generally being influenced by the presence of gross pleural contamination necessitating either direct debridement and irrigation or decortication. In patients undergoing transhiatal esophagectomy without thoracotomy, after extraction of the esophagus, the mediastinum was copiously irrigated with 3 to 6 L of saline solution.

Restoration of alimentary continuity with an immediate cervical esophagogastrostomy was carried out in 13 patients, 11 undergoing transhiatal esophagectomy and 2, transthoracic esophagectomy (see Table 1). In each patient, the stomach was positioned in the posterior mediastinum in the original esophageal bed. A pyloromyotomy and feeding jejunostomy were performed routinely in every patient. In patients undergoing a transthoracic esophagectomy with empyema drainage, the esophagus was stapled and divided above and below the site of disruption, and the damaged esophagus was removed from the field. After irrigation and debridement of the

Table 2. Esophagectomy for Esophageal Disruption: Resection With Delayed Reconstruction

Patient No.	Age (yr)	Sex	Cause of Disruption	Intrinsic Esophageal Disease	Interval From Leak to Esophagectomy	Operation	Complications	Hospitalization After Esophagectomy (days)
14	68	M	Leaking esophagogastric anastomosis, excluded esophagus	Recurrent reflux	14 days	THE/ATE	None	15
15	42	M	Leaking esophagogastric anastomosis, excluded esophagus	Carcinoma	7 days	THE/CE	None	18
16	35	F	Acute caustic ingestion	None	6 h	THE/ Gastrectomy/ CE	None	8
17	60	M	Vagotomy	None	45 days	TTE/ATE	Septic thrombocytopenia	36
18	50	M	Acute caustic ingestion	None	6 h	THE/ Gastrectomy/ CE	None	35
19	34	M	Redo hiatal hernia repair	Reflux esophagitis	4 days	TTE/CE	None	28
20	65	F	Resection of recurrent pulsion diverticulum	Spasm	4 wk	TTE/ATE	None	12
21	45	F	Spontaneous rupture	Reflux stricture	24 h	TTE/CE	None	20
22	53	M	Maloney dilation	Caustic stricture	24 h	TTE/CE	None	30
23	76	M	Leaking esophagogastric anastomosis	Carcinoma	3 days	TTE/ATE	None	27
24	27	M	Leaking esophagogastric anastomosis	Recurrent reflux esophagitis	7 days	TTE/ATE	None	11

ATE = anterior thoracic esophagostomy; CE = cervical esophagostomy; THE = transhiatal esophagectomy without thoracotomy; TTE = transthoracic esophagectomy.

pleural cavity and mediastinum, the distal esophagus was mobilized to the esophagogastric junction and the proximal esophagus, to the thoracic inlet. The chest was closed after insertion of a single large-bore chest catheter, and the patient was repositioned to the supine position with the neck extended and the head turned to the right, as for a standard transhiatal esophagectomy [8]. Gastric mobilization, pyloromyotomy, and feeding jejunostomy were then completed, and through a standard left cervical incision, the remaining intrathoracic esophagus was delivered into the neck for construction of either an esophagostomy or cervical esophagogastric anastomosis.

In the 11 patients considered too ill to undergo esophageal reconstruction at the time of esophagectomy (see Table 2), every attempt was made to preserve the maximum amount of remaining esophageal length. Once the esophagus was delivered into the cervical wound, it was tunneled subcutaneously onto the anterior upper chest wall, and an anterior thoracic esophagostomy, rather than a cervical esophagostomy, was constructed.

The 8 patients whose esophageal disruptions were complications of an esophageal procedure other than endoscopy or instrumentation (patients 13, 14, 15, 17, 19, 20, 23, and 24 [see Tables 1, 2]) were generally the most ill and presented the most difficult management problems. Often these patients had already undergone multiple operations and a prolonged hospital course elsewhere for treatment of sepsis, respiratory distress, and fluid and electrolyte imbalance. Their histories demonstrate the complexity of their problems as well as many of the pitfalls of management of perforations with esophagus-sparing procedures.

Patient 13 had undergone a Thal esophagoplasty for achalasia elsewhere 5 years before she was seen with bouts of intermittent chest pain from distention of the intrathoracic stomach. Takedown of the Thal gastric patch, repair of the esophageal mucosa, restoration of the stomach to the abdomen, and a fundoplication were performed through the left chest. Two days later, a leak of the distal esophagus occurred. The patient underwent emergent transthoracic esophagectomy with cervical esophagogastrostomy within eight hours of the occurrence of the leak. She was discharged 2 weeks later.

Patient 14 had undergone an attempted transabdominal redo Nissen fundoplication for recurrent reflux esophagitis 1 year after initial hiatal hernia repair. The gastric fundus was too devascularized for a safe fundoplication. Therefore a portion of the stomach was resected, and an esophagogastrostomy was performed under "tension" through a right thoracotomy. An anastomotic leak was evident within 24 hours postoperatively. At reoperation the esophagus and stomach had distracted. A completion gastrectomy was performed and a Roux-en-Y esophagojejunostomy attempted. The jejunum, however, would not reach the remaining esophagus, and therefore the distal esophagus was sutured closed, a nasogastric tube was placed into the remaining esophagus, and a feeding jejunostomy was performed. A septic course continued, and hematemesis occurred after 2 weeks. An esophagogram demonstrated a contained disruption of the distal esophagus in the lower mediastinum. The patient was transferred to the Thoracic Surgery Service where an emergent transhiatal esophagectomy with anterior thoracic esophagostomy was performed. The sepsis resolved, and the patient was discharged 15 days later. A substernal colonic interposition was performed after 2 months.

Patient 15 underwent a distal esophagectomy and intrathoracic esophagogastric anastomosis through a right thoracotomy and an abdominal incision for an esophageal adenocarcinoma at another hospital. Sepsis developed after 36 hours and necessitated a tracheostomy. An esophagogram showed no leak. After 1 month of intravenous antibiotics and hyperalimentation, an exploratory thoracotomy was performed. The anastomosis had disrupted, and the proximal stomach was necrotic. A completion gastrectomy and jejunostomy were performed, along with suture closure of the remaining esophagus, which was decompressed with a pharyngostomy tube. Persistent fever prompted a repeat esophagogram, which showed a contained disruption of the distal esophagus in the lower mediastinum. The patient was transferred to the Thoracic Surgery Service. A transhiatal esophagectomy and cervical esophagostomy were performed. The sepsis resolved, and the patient was discharged after 18 days. He died 1 month later of metastatic carcinoma before alimentary continuity could be reestablished.

Patient 17 underwent an emergent vagotomy and pyloroplasty for a perforated duodenal ulcer at another hospital. During the first postoperative week, sepsis developed and bilateral pleural effusions were noted. An esophagogram demonstrated a distal esophageal leak. The patient was treated with a left thoracotomy, empyema drainage, placement of a T tube in the esophageal perforation, gastrostomy, and feeding jejunostomy. The sepsis continued and was complicated by fluid and electrolyte loss through a gastropleural-cutaneous fistula that had developed. When he was transferred to the Thoracic Surgery Service 9 weeks after vagotomy and pyloroplasty, the sepsis was still present and he was ventilator dependent. He underwent a transthoracic esophagectomy, anterior thoracic esophagostomy, and empyema drainage. The sepsis gradually resolved, and he was discharged 36 days later. Nine months after the esophagectomy, a substernal gastric interposition was performed.

Patient 19 underwent a transthoracic Collis-Nissen hiatal hernia repair for recurrent reflux esophagitis 4 years after a Nissen fundoplication. Four days postoperatively, a small leak was diagnosed on an esophagogram and drained with a chest tube. The septic course continued, and eight days after the Collis-Nissen repair, a transthoracic esophagectomy, cervical esophagostomy, empyema drainage, and feeding jejunostomy were performed. A subsequent colonic interposition was done 4 weeks later.

Patient 20 underwent resection of a recurrent midesophageal pulsion diverticulum at another hospital 4 years after the initial resection. No esophagomyotomy was performed at either operation. An esophagopleural-cutaneous fistula developed within the first week after operation. Conservative therapy with antibiotics and chest tube drainage was unsuccessful. Sepsis was present and the patient was ventilator dependent through a tracheostomy when transferred to us 1 month after the diverticulum resection. An emergent transthoracic esophagectomy, decortication, empyema drainage, and anterior thoracic esophagostomy were performed. Dramatic improvement followed. The patient was discharged 12 days later, and a retrosternal gastric interposition was performed 2 months after the esophagectomy.

Patient 23, a 76-year-old man, underwent a left thoracoabdominal esophagogastrectomy for a distal esophageal adenocarcinoma at another hospital. Three days later, an anastomotic leak developed, and he was transferred to our service with mediastinitis and sepsis. An emergent transthoracic esophagectomy, anterior thoracic esophagostomy, and feeding jejunostomy were performed. The patient's condition improved, and he was discharged 27 days later. A substernal colon interposition was performed 5 months after the esophagectomy.

Patient 24 underwent a transthoracic takedown of a Nissen fundoplication, resection of a distal esophageal stricture, and a low esophagogastric anastomosis 6 years after a Hill repair and 6 months after a transthoracic Nissen fundoplication. Postoperatively, gram-negative sepsis developed and he complained of dysphagia. Dilation of the anastomosis was attempted without success. An esophagogram showed total obstruction of the distal esophagus with a leak at the anastomosis. The patient was transferred to the Thoracic Surgery Service and underwent an emergent transthoracic esophagectomy, decortication and empyema drainage, anterior thoracic esophagostomy, and feeding jejunostomy 5 weeks after the esophagogastrostomy. The sepsis resolved, and he was discharged 11 days later. A substernal colonic interposition was performed 7 weeks after discharge.

Results

Despite the presence of mediastinitis in every patient and periesophageal adhesions from prior surgical procedures in 8 patients, esophagectomy was uniformly well tolerated. Measured intraoperative blood loss for the entire group ranged from 100 to 6,000 mL and averaged 1,065 mL, 757 mL for those undergoing transhiatal esophagectomy without thoracotomy and 1,570 mL for those having transthoracic esophageal resection. Continued treatment of sepsis and hemodynamic monitoring in the intensive care unit were essential during the first one to three days after esophagectomy, as shifts of intravascular fluid frequently followed the extensive mediastinal dissection and resulting transient bacteremia for several hours.

Only 3 patients experienced complications of esophagectomy per se. One patient had an anastomotic leak. The other 2 patients had respiratory insufficiency, 1 patient with scleroderma involvement of the esophagus and lungs and the other, an 86-year-old woman, with a penetrating Barrett's ulcer.

There were three hospital deaths (12.5%) (patients 1 through 3). Two were due to continued sepsis in patients with chronic renal failure. One of them had undergone a prior renal transplantation, was on immunosuppression therapy, and had monilial esophagitis, and the other required renal dialysis. The third death occurred in the 86-year-old woman with Barrett's ulcer and a history of recent deep venous thrombosis. She died suddenly on the ninth postoperative day, presumably as the result of a pulmonary embolus despite treatment with low-dose heparin sodium postoperatively. The 21 hospital survivors of esophagectomy were discharged an average of 22 days later (range, eight to 120 days). Thirteen (62%) of the survivors were discharged in 15 days or less after esophagectomy.

For 10 of the 11 patients who underwent esophagectomy with delayed reconstruction (see Table 2), the interval between esophagectomy and reconstruction ranged from 4 to 32 weeks (average time, 8.6 weeks). In 7 of these patients, alimentary continuity was reestablished with a substernal colon interposition; in 3, a retrosternal gastric interposition was performed. As already indicated, patient 15 died of progression of esophageal carcinoma before reconstruction could be carried out.

Of the 21 hospital survivors of esophagectomy for perforation, 2 died without being able to eat, 1 of pneumonia at a nursing home 4½ months after operation and the other of metastatic distal esophageal cancer 2 months after esophagectomy. Four patients ate well until they died of suicide, myocardial infarction, myocardial infarction, and colon cancer at 4 months, 18 months, 32 months, and 42 months, respectively, after esophagectomy. The remaining 15 patients have been followed from 1 month to 96 months (average follow-up, 31 months). Intractable postvagotomy diarrhea developed in 1 of these patients, who had irritable bowel syndrome before esophagectomy, and he has not been able to nourish himself well despite patency of the substernal colonic interposition. He requires intravenous hyperalimentation at home 42 months after esophagectomy. The other 14 patients have done well. They can maintain a stable weight and are able to eat normal diets with minimal postvagotomy diarrhea, early satiety, regurgitation, or diarrhea.

Comment

In each of our 24 patients with disruption of the intrathoracic esophagus, the risk of esophageal resection was thought to be less than the consequences of attempted primary repair, drainage, or diversion. An esophageal suture line proximal to an obstruction is at risk for disruption unless adequate relief of the distal block can be achieved. A quickly diagnosed distal esophageal perforation proximal to a dilatable reflux stricture can be treated successfully with intraoperative bougienage, closure of the tear, and buttressing of the suture line with an intercostal muscle pedicle, pericardial flap, or omentum [9–11]. Similarly, when pneumatic dilation results in a tear in an esophagus with achalasia, esophagomyotomy and repair of the tear can be successful.

In contrast to these more "favorable" situations, a perforation occurring in a patient with a severe "hard" reflux stricture that is difficult to dilate, a megaesophagus of achalasia, a caustic stenosis, or an esophageal carcinoma is unlikely to be repaired successfully. Michel and associates [4] reported a 23% mortality rate for patients with perforations associated with intrinsic esophageal disease compared with 4% for those with perforations in an otherwise normal esophagus. Disruption of the attempted primary closure after the patient has already undergone one major thoracic operation inflicts recurrent mediastinitis and the need for reoperation on a patient whose condition is already debilitated, and is a major source of morbidity and mortality [12, 13]. It is our belief that in such patients, the more major initial operation, ie, esophageal resection, is more reliable and therefore safer therapy in the long run. It eliminates the source of the intrathoracic sepsis (the leak) as well as the diseased esophagus.

In general, we avoid any type of esophageal exclusion in the patient with a perforation [14, 15], as these approaches only complicate subsequent reconstructive procedures. Occluding tapes around the esophagogastric junction must eventually be removed. Dividing the disrupted intrathoracic esophagus and stapling or suturing closed the distal end in the middle or lower mediastinum in an infected field sets the stage for potential disaster when the closure leaks several days later (as occurred in patients 14 and 15). A lateral or end-cervical esophagostomy constructed after division of the upper esophagus creates definite technical problems for subsequent esophageal reconstruction.

When the patient's general condition or the extent of pleural or mediastinal contamination are thought to preclude a safe one-stage esophagectomy and reconstruction, *the safest esophagostomy is an end-esophagostomy*, and the maximum length of viable esophagus proximal to the tear should always be preserved. By tradition, a cervical esophagostomy has been "tailored" to the neck incision, and viable esophagus has been discarded in the construction of an esophageal stoma on the side of the neck or in

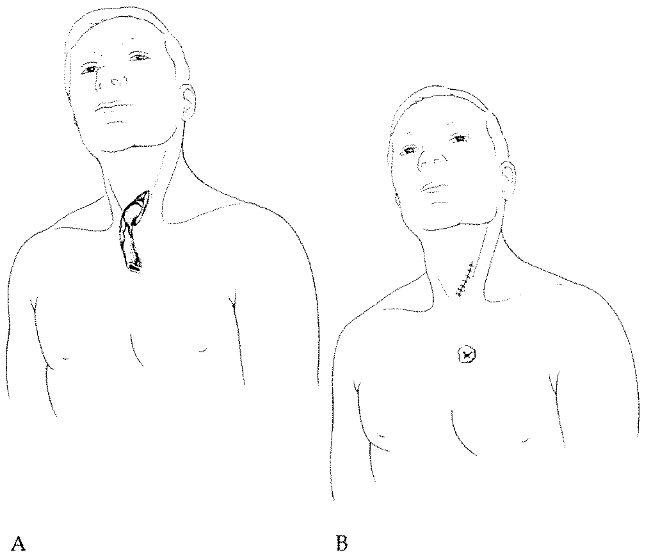


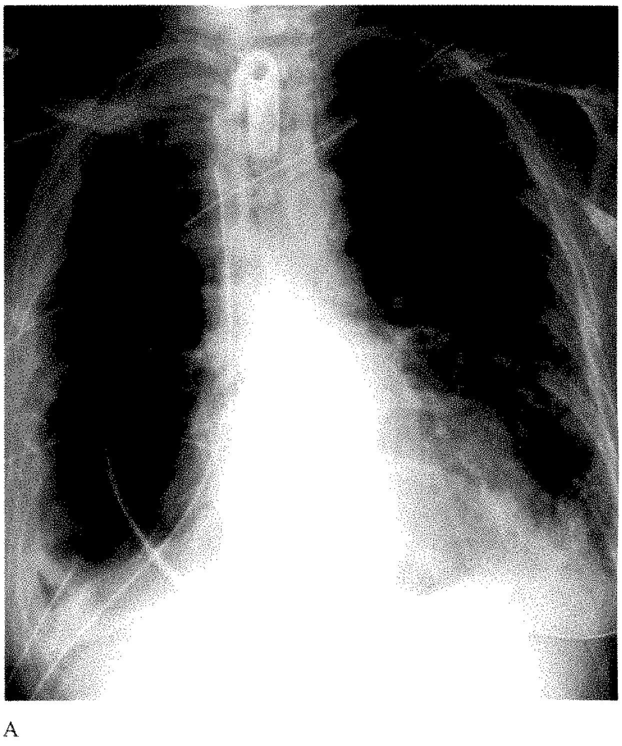
Fig 1. Construction of anterior thoracic esophagostomy after esophagectomy for esophageal disruption. (A) Rather than discarding viable esophagus that has been mobilized through the cervical incision, (B) the remaining esophagus is tunneled subcutaneously and a stoma is constructed on the upper anterior thorax. (Reproduced with permission from Orringer MB [9].)

the supraclavicular fossa. Control of the resulting salivary fistula is difficult and cumbersome for the patient, who often finds it awkward to apply a stomal appliance to the lateral or lower neck areas.

In recent years, when a proximal esophagostomy has been required, we have preserved the maximum remaining length of esophagus proximal to the tear; this length can be 8 to 12 cm. The extensive submucosal vascular collateral network of the esophagus, now based on the thyroid arteries, inevitably maintains viability of this segment of the esophagus, which is tunneled subcutaneously over the clavicle for construction of a high anterior thoracic cervical esophagostomy (Fig 1). An esophageal stoma in this location is far easier to care for, as stomal appliances are more readily placed on the flat surface of the upper chest. Further, when retrosternal esophageal replacement is eventually undertaken, the relatively long remaining length of upper esophagus minimizes the required superior reach of the transposed colon or stomach.

The operative approach for esophagectomy in the patient with an esophageal leak—transthoracic versus transhiatal—is dictated by the chronicity of the tear and associated mediastinitis as well as the presence and degree of pleural contamination. For example, patient 20 (Fig 2) had undergone two right thoracotomies with diverticulum resections and was treated for 4 weeks with chest tube drainage of the resulting esophagopleural-cutaneous fistula. A transthoracic approach was required to resect the esophagus from the periesophageal mediastinal reaction and to decorticate the right lung.

Alternatively, a transhiatal esophagectomy without thoracotomy is an excellent approach to use within the first several hours of an esophageal tear when there is



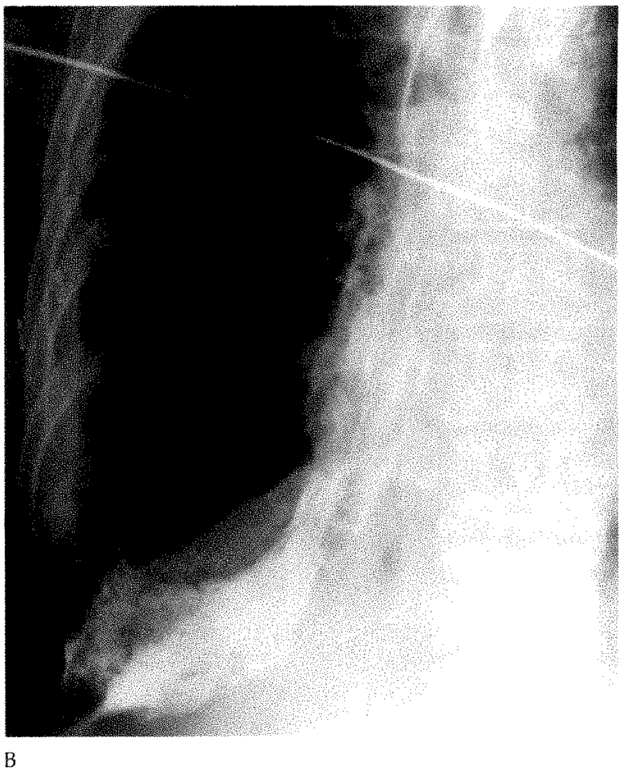


Fig 2. (A) Chest roentgenogram of patient 20, who was transferred to us with a tracheostomy, left-sided pneumonia, and sepsis from the right esophagopleural-cutaneous fistula, which followed a midesophageal diverticulum resection that had been treated with chest tube drainage for 4 weeks. (B) Gastrografin (diatrizoate meglumine and diatrizoate sodium solution) esophagogram showing a large leak with no passage of contrast medium through the distal esophagus. A transthoracic esophagectomy was performed

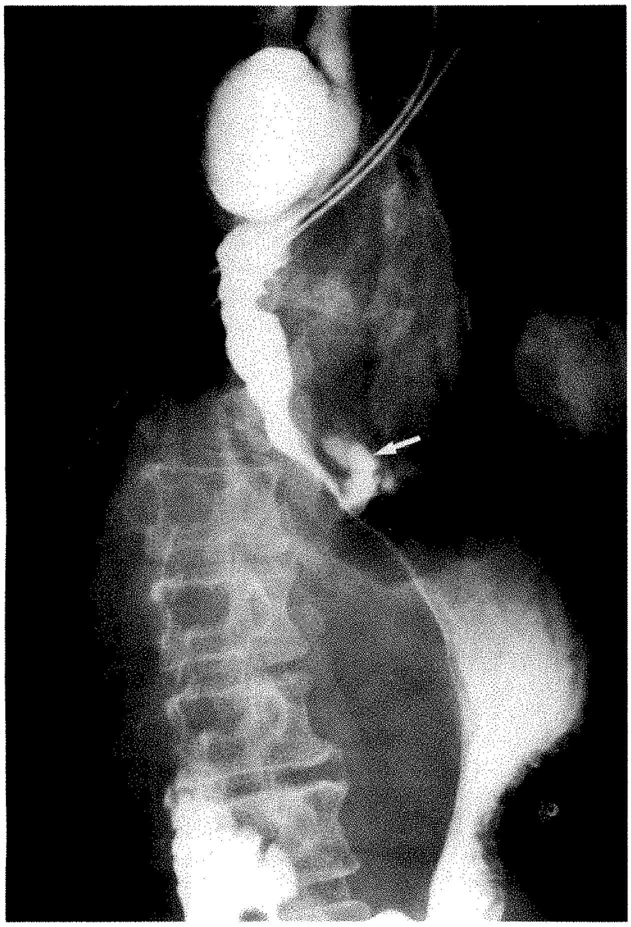


Fig 3. Gastrografin (diatrizoate meglumine and diatrizoate sodium solution) esophagogram in patient 9, who sustained a distal perforation (arrow) *during balloon dilation. Repair of the tear and treatment of the underlying neuromotor dysfunction with an esophagomyotomy and diverticulum resection would have left this patient with two esophageal suture lines in a potentially contaminated field. Transhiatal esophagectomy, mediastinal irrigation, and cervical esophagogastric anastomosis were performed.*

minimal pleural contamination or when the leak is confined to the mediastinum (Fig 3). Intraoperative mediastinal and pleural irrigation through the diaphragmatic hiatus and the cervical incision after extraction of the esophagus effectively cleanses the contaminated areas, and, if the patient's condition permits, mobilization of the stomach through the posterior mediastinum for a cervical esophagogastric anastomosis can be performed.

The thesis of this report is *not* that any patient with an esophageal perforation should be treated with an esophagectomy. However, in our experience, the more critically ill the patient with an intrathoracic esophageal disruption, particularly when attempted drainage, closure, or exclusion has failed to control sepsis, the more compelling the argument for esophageal resection. This approach may be the only hope for completely ending continued mediastinitis, pleural contamination, and loss of saliva and gastric juice through the fistula. In other words, the patient may simply be too sick to have anything but an esophagectomy. Of our 5 oldest patients (ages 76, 78, 79, 86, and 88 years), only 1 died after esophagectomy; the death was probably the result of a pulmonary embolus.

Conservative nonoperative management of intrathoracic perforations localized to the mediastinum and not associated with pleural contamination or sepsis has been advocated [16, 17]. Others [18] argue that a thoracotomy to control an esophageal leak in a desperately ill patient is unwise. Most authors [3, 4, 19], however, believe that an esophageal leak should be controlled to prevent continued contamination of the perforation site with subsequent development of a mediastinal abscess and empyema, and that conservative treatment with chest tube drainage is inadequate. Grillo and Wilkins [20] advocated use of a flap of the adjacent thickened, inflamed parietal pleura to buttress late intrathoracic esophageal perforations. T-tube drainage of the esophagus to establish a controlled esophagopleural-cutaneous fistula [21] and occlusion of the leak with an endoesophageal prosthesis [1, 22] have also been reported. These options are fine if the esophageal leak and associated contamination are controlled. Their drawback, however, is obvious: a recurrent esophageal leak can be fatal.

Successful esophagectomy and esophagogastrostomy after instrumental perforation of the thoracic esophagus has ample precedent [23, 24]. Others [25, 26] have opposed this approach because of a high rate of anastomotic leak in the presence of mediastinitis. However, with contained mediastinal contamination in a patient in otherwise stable condition, a transhiatal esophagectomy followed by vigorous mediastinal irrigation and one-stage cervical esophagogastrostomy has definite advantages. The posterior mediastinal "space" is filled by a well-vascularized, resilient organ, and the anastomosis is performed out of the contaminated field, thereby minimizing the risk of anastomotic leakage.

The choice of operative approach in the patient with an esophageal perforation requires critical assessment of the patient's overall status, the duration of the leak, the extent of mediastinal and pleural contamination, the presence of intrinsic esophageal disease, and surgical judgment as to the likelihood of a successful repair and the patient's ability to tolerate the consequences of yet another esophageal disruption. Esophagectomy in the critically ill patient with mediastinitis and sepsis may not be the appropriate choice if the surgeon lacks familiarity and training in the management of complex esophageal problems. However, we believe that this option, as radical as it may seem, may prove to be the safest and more conservative approach in many of these gravely ill patients.

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DISCUSSION

DR JOSEPH S. McLAUGHLIN (Baltimore, MD): A few years ago Dr Orringer and I and others sat on the Self-Education/Self-Assessment in Thoracic Surgery Committee, and one of the questions that came up was what to do about esophageal perforation. It was the consensus that esophageal resection was at times indicated but we were unable to define clearly what were the indications for resection. So Dr Orringer and I went home and, like proper academic surgeons, looked up our experiences. His report, which I had the privilege of reading earlier, goes a long way toward defining the use of what may seem to be a radical procedure in this situation.

In our series of 65 patients treated over the past 20 years there were 20 cervical perforations, 44 thoracic perforations, and one abdominal perforation. These patients were treated in a variety of ways. The patients with cervical perforation were treated simply by primary closure and drainage, often just by drainage. Those that went past 24 hours often required pleural drainage as well because of mediastinitis and empyema.

The patients with thoracic perforation were treated by primary closure of the esophagus, often with pleural patch reinforcement and drainage, exclusion operations, and pleural and mediastinal drainage; 8 were treated with total esophagectomy, which I shall comment upon in a moment.

With this balanced approach, within 24 hours most patients do well. Ninety percent with cervical perforations survive. After 24 hours, all bets are off and the patients do much worse; only 63% survived.

In the group with thoracic perforation, 15 of 18 patients treated within 24 hours survived: many of these were treated by primary closure, an 83% survival rate. Once again, after 24 hours, the mortality rate markedly increased so that only 54% of the patients survived. The total survival was 70% of those patients treated.

My associates—Drs Attar and Hankins—in looking up our data identified 8 patients who underwent esophagectomy for perforation. Three of these patients had caustic stricture—they were dilatation catastrophes—3 others were patients who swallowed lye, often in a suicide attempt, and 2 were patients who had perforations in association with malignancy. It is not a very large series but an interesting one. Five of the patients had transthoracic esophagectomy, 3 of whom later came to staged colon transposition: 4 of these 5 patients survived. One patient died a month or two later from necrosis of the pancreas from the caustic ingestion. Three patients had transhiatal esophagectomy and 2 of these patients survived. The patient who did not survive had carcinoma of the esophagus and died about 6 weeks later. So 6 of the 8 survived for a rate of 75%.

I ask Dr Orringer to comment on a couple of items. First, would you comment on immediate as opposed to staged reconstruction? I think that is a critical issue. How do you resolve this issue?

Second, the last statement of the abstract is "the decision to restore alimentary continuity in a single stage must be individualized." How do you individualize? I believe it is important that we understand how you do this yourself under various circumstances.

Finally, and as an interesting question for us because 1 of our patients died in this situation, what do you do for a patient who has a perforation and who has what appears to be an established empyema?

DR ORRINGER: The decision for immediate versus staged reconstruction after esophagectomy is an individual decision that is based on the presence of preexisting sepsis and the overall condition of the patient. We have had good luck with patients, even those with 2-week or older perforations confined to the mediastinum, treated with transhiatal esophagectomy and irrigation and then one-stage esophageal replacement with stomach.

Patients who have had a previous transthoracic operation, for example, an intrathoracic esophagogastrostomy, complicated by a leak that has produced severe sepsis, have undergone a completion transthoracic esophagectomy, irrigation of the chest, and decortication with later reconstruction depending on when they recover sufficiently from the physiological insult of their mediastinitis.

In the management of an esophageal perforation associated with an established empyema, control of the empyema clearly has priority. In these patients, we would most often opt to decorticate the lung, clean out the empyema, and then eliminate the source of the empyema, which is the leak, by doing an esophagectomy. We then perform an anterior thoracic esophagostomy and feeding jejunostomy and come back another day when the patient has recovered from this physiological insult. This is a controversial area that still needs to be further defined, but we are convinced that some of these patients are simply too ill not to have their esophagus removed and their mediastinitis controlled, and this philosophy has been the basis for this report.

Important Notice From the American Board of Thoracic Surgery Regarding Approved Training

The American Board of Thoracic Surgery will no longer accept training in thoracic surgery obtained in residency programs that are not approved by the Residency Review Committee for Thoracic Surgery of the Accreditation Council for Graduate Medical Education. This policy will apply to residents initiating training after July 1, 1990. Notification of this policy has been sent to all program directors. If you wish to obtain further information, please contact the Board office.

Direct Revascularization of Bronchial Arteries for Lung Transplantation: An Anatomical Study

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Baron D. Harper, MD, Shinji Shimokawa, MD, Thomas M. Egan, MD,
Robert McKnight, MD, and Joel D. Cooper, MD

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Direct revascularization of the bronchial arteries for both single-lung and double-lung transplantation would improve airway healing and reduce airway complications after transplantation. We studied the anatomical pattern of bronchial arteries in 30 autopsy cases. In 28 of 30 cases (93.3%), at least one left bronchial artery arose directly from the anterior wall of the descending thoracic aorta. In 25 of the 30 cases (83.3%), at least one right bronchial artery was related to the first right intercostal artery. Injection studies showed that this right intercostobronchial artery supplies the proximal left main bronchus and carina as well as the right bronchus. We developed a technique for extracting the lungs along with the right intercostobronchial artery and a patch of aorta at its origin and applied it to 19 of the dissections. In 17 of the 19 cases studied (89.4%), the right intercostobronchial artery pedicle obtained had a length varying from 6.5 to 8.5 cm, sufficient for attachment of its origin to the ascending aorta of the recipient after double-lung transplantation. The right intercostobronchial artery pedicle provides the possibility for direct bronchial revascularization in right single-lung, double-lung, and lung-heart transplantation. A similar technique, utilizing the left bronchial artery, can be used to revascularize a left lung transplant.

(Ann Thorac Surg 1990;49:44–54)

In the 20 years after the first human lung transplantation in 1963 by Hardy and associates [1], complications of the bronchial anastomosis has been the most common cause of death in lung transplant recipients who survived more than 2 weeks. We have used an omentum pedicle wrapped around the bronchial anastomosis to restore bronchial artery circulation [2] for both single-lung and double-lung transplant procedures. Nevertheless, serious airway complications still arise [3], including ulceration, partial necrosis, dehiscence, and late stenosis. None of our initial 16 single-lung transplant recipients died as a result of airway complications. We recently reviewed our initial double-lung transplant experience, however, which has a mortality rate of 25% as a result of tracheal complications and another 20% rate of delayed airway stenosis requiring special treatment. Use of direct revascularization would provide immediate systemic blood supply to the tracheobronchial tree of the transplanted lung and would likely decrease or eliminate the early and late airway complication rate. Therefore, we evaluated the possibility of establishment of direct revascularization of the donor's right and left bronchial arteries into the recipient's ascending or descending thoracic aorta.

Material and Methods

Anatomical dissections were undertaken in an unselected series of 30 autopsies, excluding cases with a history of a thoracic surgical procedure. To simulate the "donor" situation, we used a median sternotomy. The heart was initially removed by the technique we described previously for separate heart and lung extraction for transplantation of both organs [4].

Technique of Harvesting Autopsy Lung-Heart Blocs Together With Bronchial Arteries

The right intercostobronchial artery originates from the right lateral wall of the descending thoracic aorta as a common trunk for the first or second right intercostal artery and a right bronchial artery. It divides into the intercostal artery and a right bronchial artery at a variable distance from the aorta. The intercostobronchial artery crosses to the right, posterior to the esophagus. Its bronchial branch then courses between the esophagus and azygos vein extrapleurally and continues superiorly and anteriorly toward the right main bronchus. This anatomy necessitated extraction of the lung bloc in toto with the thoracic aorta, esophagus, part of the right-sided pleura covering the azygos vein, and all the posterior mediastinal fatty tissue immediately anterior to the vertebral bodies in which the artery is embedded. The arch of the azygous vein is an important, constant landmark for the anterior course of the bronchial branch of the intercostobronchial artery (Fig 1). The superior vena cava was ligated and transected both above and below this level, thus preserving the azygos arch, vein, and underlying intercostobron-

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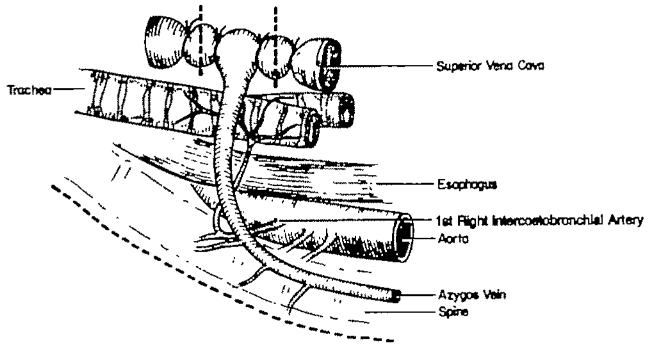

Fig 1. Schematic view of the mediastinum from the right chest showing relationship of first right intercostobronchial artery and right bronchial artery to azygos vein and arch of azygos vein. The oblique dotted line *represents the cut of the posterior mediastinal pleura at the costovertebral junction during organ retrieval. The* vertical dotted lines *represent the division of the superior vena cava above and below the level of the azygos vein.*

chial artery. Next, the great arteries arising from the arch of the aorta were ligated and transected. The transection of the bracheocephalic trunk provided an excellent approach to the trachea at a high level. The trachea was ligated and transected as high as possible to avoid damage to the bronchial arteries by traction. The esophagus was ligated and transected at the same level. The descending aorta and esophagus were isolated as distally as possible in the chest, ligated, and transected after the diaphragmatic pericardium was mobilized. The mediastinal pleura between the sternum and trachea was transected on both sides at the level of the clavicle. The only remaining connection between the lung bloc and the chest wall was then the posterior mediastinum.

Figure 2 shows the relationship between the intercostal arteries, aorta, vertebral column, and pleura. The distance between the aorta and the division of the right intercostobronchial artery varied in our series from 1.5 to 5.5 cm. To avoid injury to the intercostobronchial artery, the first cut in the posterior mediastinal pleura was made on the right side at the level of the costovertebral junctions, from caudally to high up cranially (Fig 3A). The second cut in the pleura was made on the left side 1 cm posterior of the aorta, caudally to cranially (Fig 3B). The third cut was made as cephalad as possible, transversely over the spine, connecting both forementioned longitudinal cuts. Then, from the left to the right side, all fatty tissue overlying the vertebral column was sharply excised, together with the lung bloc (Fig 3C).

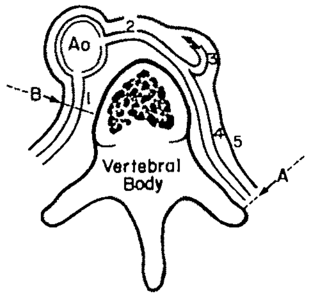

Fig 2. Relationship between the intercostal arteries, the aorta, vertebral column, and pleura. (1 = left intercostal artery; 2 = right intercostobronchial artery; 3 = right bronchial artery; 4 = right intercostal artery; 5 = pleura; A = level of incision of right posterior mediastinal pleura; B = level of incision of left posterior mediastinal pleura; Ao = descending thoracic aorta at level T5-6.)

Using this technique of excision of the lung bloc, we concentrated our efforts in studying anatomy of the posterior bronchial arteries originating directly from the aorta or from intercostal arteries, which provide by far the most important systemic blood supply to the tracheobronchial tree and lungs. We gave no attention to anterior bronchial arteries, which may arise occasionally from the subclavian artery or mammary artery. Angiography revealed the anatomy of the bronchial arteries in each specimen. After the angiographic studies of the separate bronchial arteries in the first 11 dissections, we developed a technique to isolate the right bronchial artery with the intercostobronchial artery pedicle and used it in the last consecutive 19 dissections. In the last five of these dissections, a left bronchial artery pedicle was separately isolated in addition to the right intercostobronchial artery pedicle.

Technique of Preparation of Right Intercostobronchial Artery Pedicle for Double-Lung or Lung-Heart Transplantation

After the specimen was excised, it was placed on the preparation table with the posterior aspect up (Fig 3D). The posterior surface of the descending thoracic aorta was marked at a level 3 cm above and 3 cm below the level of the arch of the azygos vein to isolate a segment of the descending thoracic aorta containing the orifice of the first or second intercostobronchial artery, or both. The aorta was transected at the levels marked (Fig 3D). The arch of the aorta was dissected free and discarded, care being taken not to injure the left pulmonary artery. Next the distal aorta was freed from the esophagus and discarded. The remaining isolated segment of the descending thoracic aorta was retracted to the right side, and cautery was used to dissect down to the left posterior aspect of the esophagus, which inevitably included division of the left bronchial arteries (Figs 4A, 4B). The aortic segment was then reflected further to the right, taking with it all tissue posterior to the wall of the esophagus. The esophagus was then freed over its entire length as close as possible to the muscular layer under slight traction and without damaging the underlying bronchi and carina (Fig 4C).

The aortic segment was then opened longitudinally on the left side close to the left intercostal artery orifices. The first and second right intercostobronchial arteries were identified. Both originate from the aortic wall from the two upper paired intercostal arteries. The intercostobronchial artery usually has a larger orifice in the descending aorta than the other intercostal arteries (Fig 5).

We developed a device to provide continuous pressure-controlled perfusion of the intercostobronchial artery without having to cannulate the vessel, which might damage the intima (Fig 6). This perfusion allows identification of disrupted vessels, which are ligated, clipped, or cauterized, depending on their size. It also helps in

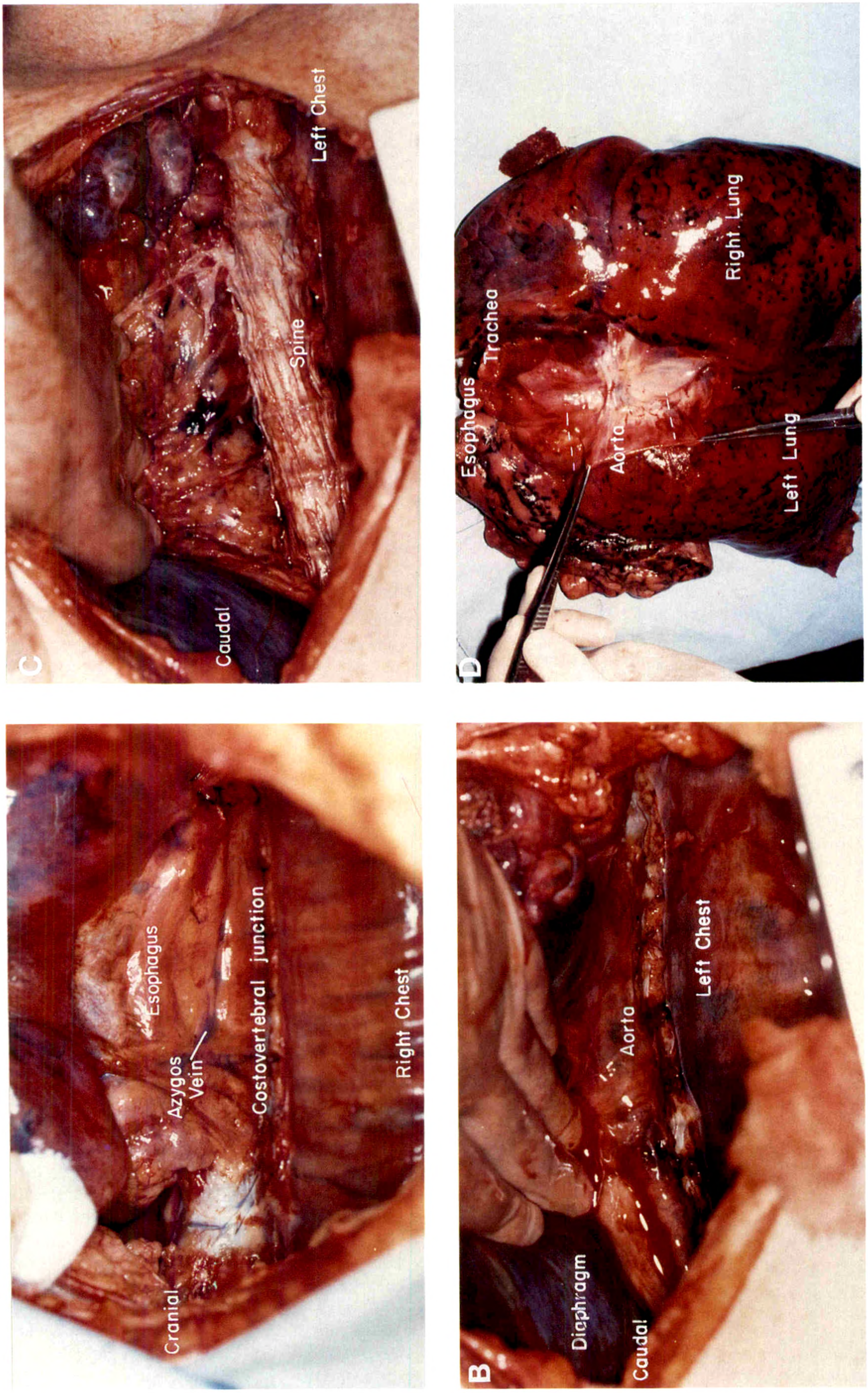

Fig 3. Technique of retrieving heart-lung bloc together with the bronchial arteries. (A) First incision in the posterior mediastinal pleura on the right side at the level of the costovertebral junction. (B) Second incision in the posterior mediastinal pleura on the left side posterior of the aorta. (C) Completed posterior dissection: tissue in front of the spine has been sharply dissected from the vertebral bodies from the left to the right side. (D) Posterior view of excised specimen. The dotted lines mark the segment of the aorta containing the bronchial arteries.

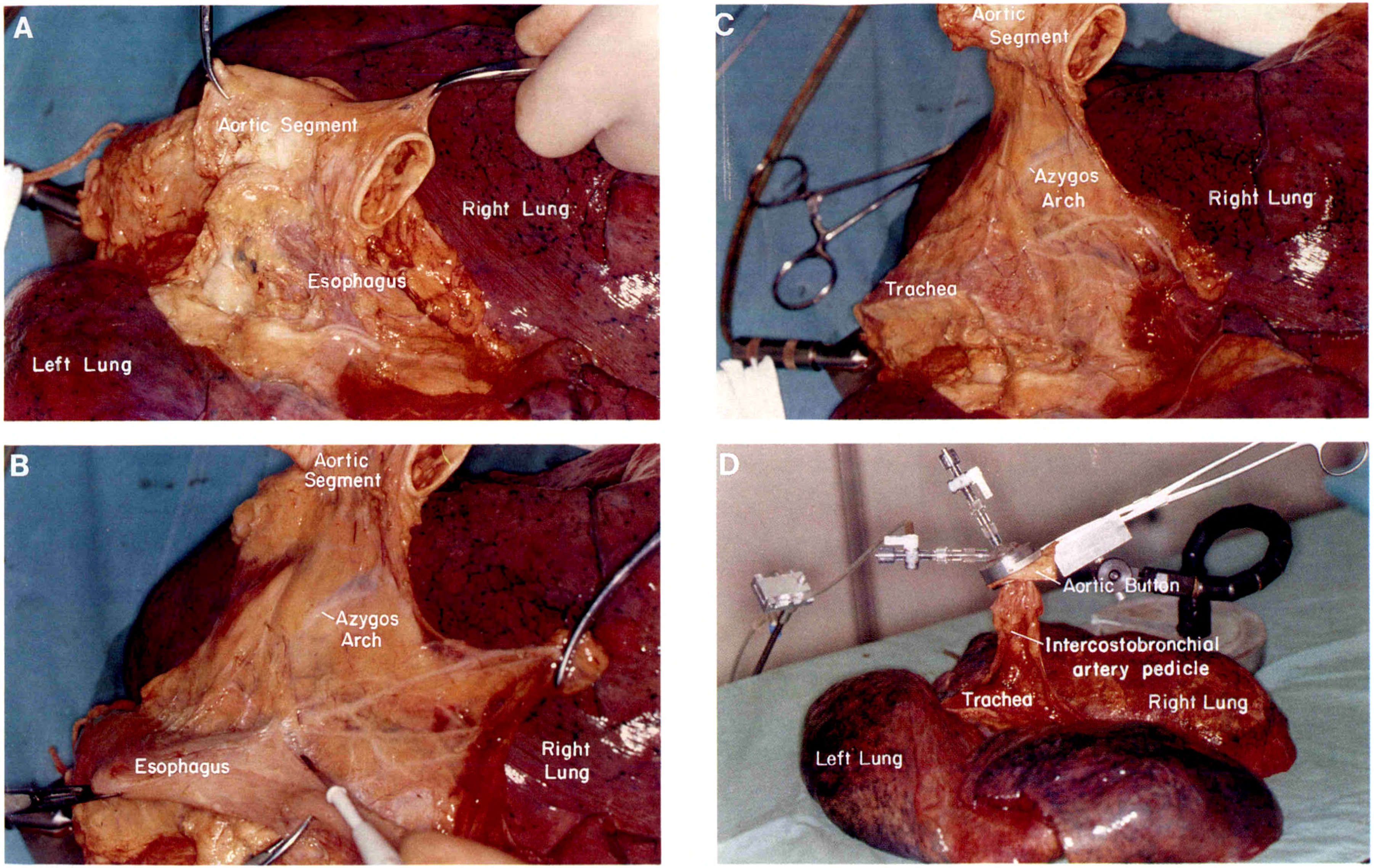

Fig 4. Technique of preparation of the right intercostobronchial artery pedicle for double-lung or heart-lung transplantation. (A) Isolated aortic segment containing the right intercostobronchial artery is reflected toward the right: tissue between the aorta and left posterior wall of the esophagus is dissected. (B) Dissection of the esophagus. (C) Specimen after the esophagus has been removed. (D) Origin of the pedicle incorporated into the holder.

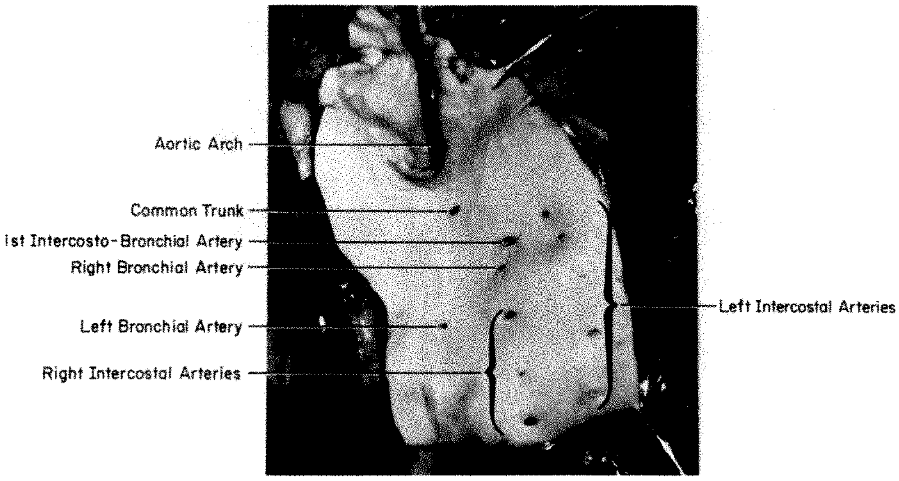
Aortic Arch
Common Trunk
1st Intercosto-Bronchial Artery
Right Bronchial Artery
Left Bronchial Artery
Right Intercostal Arteries
Left Intercostal Arteries

Fig 5. Aortic segment is opened longitudinally on the left side. The orifice of the first right intercostobronchial artery is usually larger than the orifice of the intercostal arteries.

identification of the main vessels by palpation during administration of pulsatile flow from the perfuser. Next an aortic button was prepared by dissection of the adventitia of the aorta around the origin of the intercostobronchial artery. An aortic patch containing the vessel was prepared and placed in the perfusor clamp (Fig 4D). Then the pedicle was freed down to its junction with the right side of the trachea, two rings above the carina. After preparation of the pedicle for implantation, we ligated the azygos vein distally but left it in position to strengthen the pedicle.

Technique of Preparation of Right Intercostobronchial Artery and Left Bronchial Artery for Single-Lung Transplantation

After the specimen was excised, it was placed on the preparation table with the posterior aspect up (Fig 3D). The aorta was opened longitudinally on its left lateral wall close to the left intercostal artery orifices. The orifice of the intercostobronchial artery was identified as described before. The orifice of the left bronchial arteries was usually located in the anterior wall of the descending thoracic aorta at a level between the arch of the aorta and the third paired intercostal arteries (Fig 5). Its orifice in the aorta was directly posterior to the membranous aspect of the left main bronchus. Next, a segment of aorta was marked at a distance above and below the orifices of the right intercostobronchial and left bronchial arteries, which allowed a sufficient button of aorta for each artery. The aorta was transected at the marked level. Next, this aortic segment was split longitudinally or transversely according to the level of origin of the bronchial arteries (Fig 7). The segment containing the right intercostobronchial artery was then freed to the right side posteriorly to the esophagus in a way similar to that previously described for double-lung transplantation. In single-lung transplantation, the aortic origin of the right intercostal bronchial artery would be reimplanted, probably in the innominate or subclavian artery. The segment containing the left bronchial arteries was freed to the left side. For both left and right bronchial artery preparation, the esophagus was freed as close as possible to the muscular layer under slight traction and without damaging the underlying bronchi. Preparation of the aortic button containing the orifice of the left bronchial artery was similar to preparation of the aortic button containing the orifice of the right intercostobronchial artery. After a button of the aorta containing its orifice was freed, the left bronchial artery was freed from its connections with the left main bronchus up to the level selected for transection of the donor left main bronchus. It was then attached to the pedicle perfusor and prepared for implantation. In a left single-lung transplantation, the left pedicle button would be reimplanted in the recipient's descending thoracic aorta, adjacent to the left main bronchus.

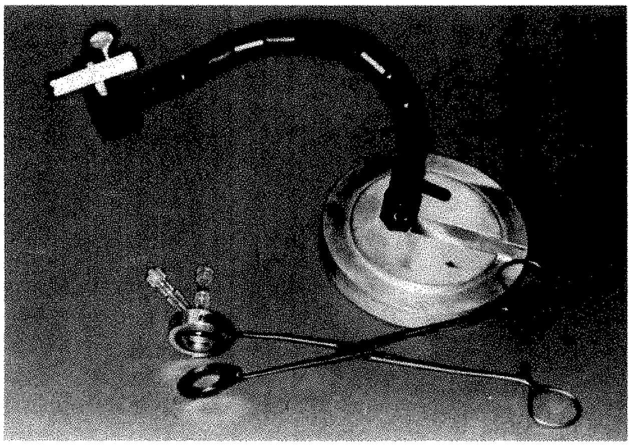

Fig 6. Device for continuous pressure-controlled perfusion of the intercostobronchial artery without the need to cannulate the vessel. The aortic button will be sandwiched between a disc and a dome through which flushed solution can be infused under pressure as shown in Figure 4D.

Results

Anatomical Patterns

The most common pattern of bronchial artery distribution was one right and two left bronchial arteries (26.6%), followed by two right and two left bronchial arteries

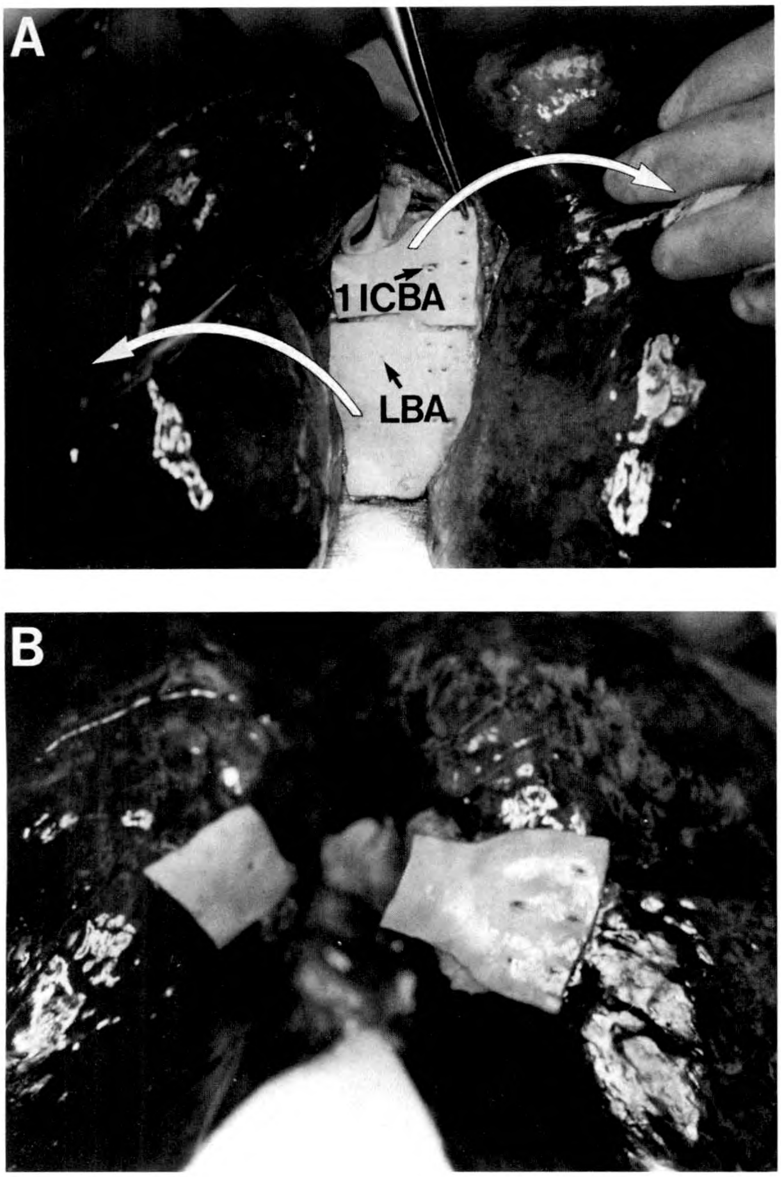

Fig 7. Technique of separate preparation of right intercostobronchial artery and left bronchial artery for single-lung transplantation. (A) The aortic segment is split transversely. Black arrows *show origin of the bronchial arteries.* White arrows *indicate the freeing of the left bronchial artery* (LBA) *toward the left and the first right intercostobronchial artery* (1ICBA) *toward the right. (B) Both pedicles freed.*

(20%). The data for the anatomy in the 30 cases are summarized in Figure 8.

In 28 of 30 cases (93.3%), at least one left bronchial artery originated from the anterior wall of the descending thoracic aorta. In 7 cases (23.3%), there was a common trunk with a right and a left bronchial artery originating from the anterior wall of the descending thoracic aorta. In 5 cases (16.6%), a left bronchial artery was related to a right intercostal artery. In four of these 5 cases, a left and right bronchial artery arose in a common trunk from a right intercostal artery. A left bronchial artery was never related to a left intercostal artery. In 7 cases, a small artery originated distally very close to the arcus aorta supplying the subcarinal lymph nodes and carina, described as the subcarinal artery.

In 27 of 30 patients (90%), at least one right bronchial artery was related to a right intercostal artery. In 25 patients (83.3%), a right bronchial artery was related to the first right intercostobronchial artery. A right bronchial artery was never related to a left intercostal artery. Table 1 shows a literature survey of intercostal artery–related right bronchial arteries, emphasizing the consistency of the right intercostobronchial artery.

Of the 19 dissections in which preparation of a right intercostobronchial pedicle was attempted, a right intercostobronchial artery pedicle was obtained in 17 (89.4%), with a length varying from 6.5 to 8.5 cm. In 5 of the 19 dissections, preparation of a left bronchial artery pedicle was attempted and was successful in all cases, with a length varying from 2.5 to 4.5 cm.

Injection Studies

The distribution of circulation from the bronchial arteries to the tracheobronchial tree was studied to evaluate its importance in tracheal and bronchial viability in lung transplantation. After the specimen was excised, it was placed on the preparation table with the posterior aspect up. In the first 11 specimens (specimens 1–11, Fig 8), all

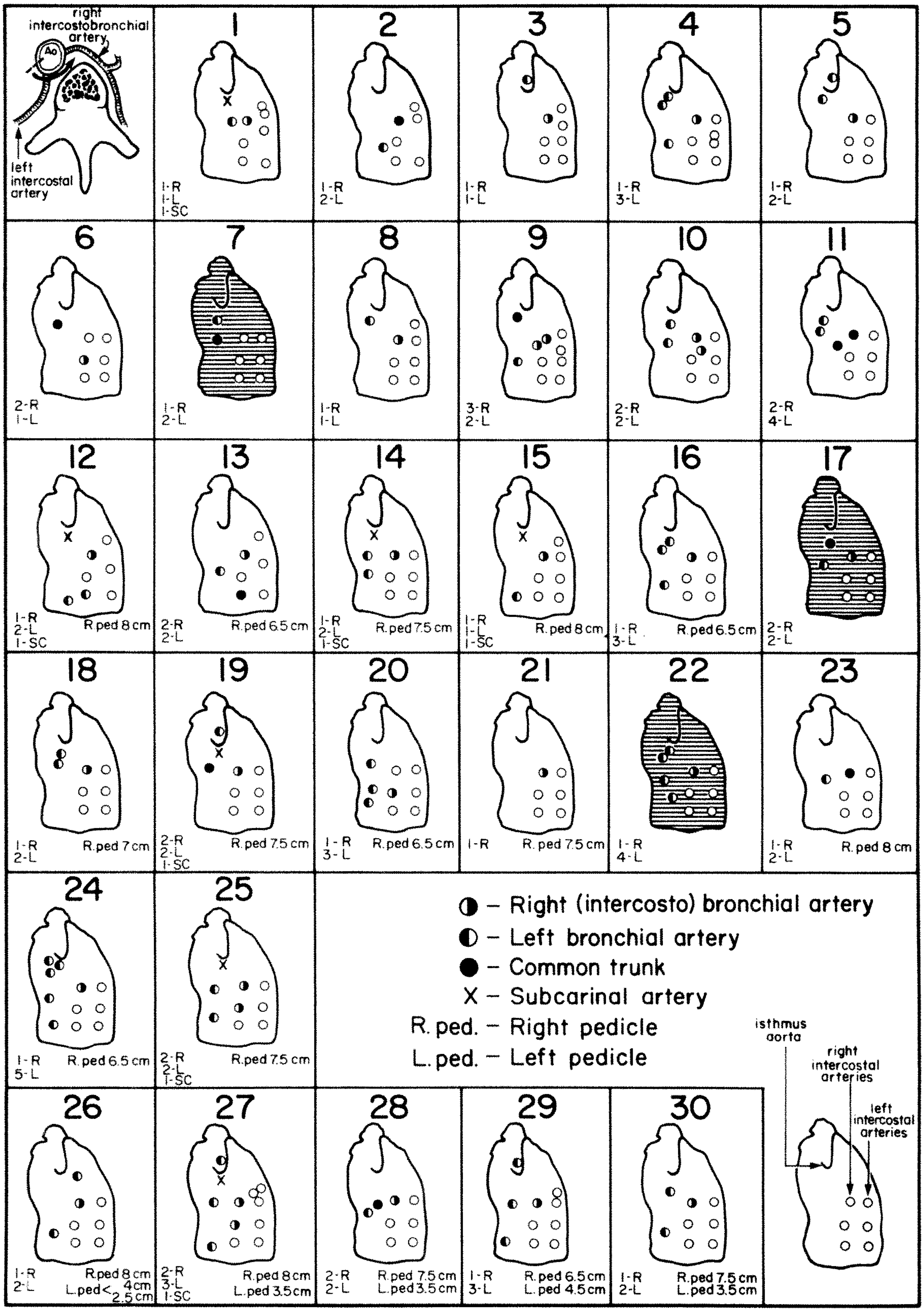

Fig 8. Survey of anatomy of posterior bronchial artery pattern in 30 autopsy studies. Left upper diagram shows incision into aorta (dotted line) *to visualize its inner aspect. Gray diagrams did not contain an intercostobronchial artery. (L = left bronchial artery; R = right bronchial artery; SC = subcarinal artery.)*

Table 1. Survey of Incidence of Intercostal Artery–Related Right Bronchial Arteries

Author	Reference	Year	No.	%
Nakamura et al	5	1924	106/129	82.1
Cauldwell et al	6	1948	133/150	88.7
Liebow	7	1965	37/50	74.0
Nathan et al	8	1970	60	"almost all"
Kasai and Chiba	9	1979	34/40	85.0
Schreinemakers et al	Present study	1990	27/30	90.0

possible orifices in the thoracic descending aorta of the right intercostal arteries as well as the arteries originating from the anterior wall of the thoracic ascending aorta were cannulated with a 5F catheter and injected with hypaque 76 (diatrizoate meglumine). In 10 of 11 specimens, a right intercostobronchial artery was found, and in 10 of 11, at least one left bronchial artery arose from the anterior wall of the aorta. These 11 specimens were then used to develop the technique for preparation of the right intercostobronchial artery pedicle. In the next 14 specimens (specimens 12–25, Fig 8), we attempted to isolate the right intercostobronchial artery before performing injection studies of the bronchial arteries. In 12 of 14 specimens, a right intercostobronchial artery pedicle could be produced. After preparation of this pedicle, injection studies were performed through this pedicle and the remaining orifices in the thoracic descending aorta. In 13 of 14 specimens, at least one left bronchial artery originated from the anterior wall of the aorta. In the last five specimens, we attempted to isolate a right intercostobronchial artery pedicle as well as a left bronchial artery pedicle. In all five specimens, both pedicles could be isolated. After preparation of both pedicles, injection studies were performed through these pedicles and the remaining orifices in the thoracic descending aorta. At least one left and one right bronchial artery could be demonstrated in these five specimens by such angiographic study. In 5 of 30 specimens, a left bronchial artery originated from the aortic arch. Cineangiography showed a rich collateral network between the separate left and right bronchial arteries, even after preparation of the right intercostobronchial artery pedicle. Figure 9 shows a close view of a prepared, injected pedicle. The collaterals to the left main bronchus, subcarinal area, and carinal area are clearly visible. Methylene blue injection studies of the isolated intercostobronchial artery pedicles showed mucosal coloring in the right and left main bronchus, the carina, and the distal rings of the trachea.

Comment

Anatomists [5–9] have documented the variability in origin of the bronchial arteries. For our purposes, we wished to define the degree of consistency. At least one left bronchial artery arose from the anterior wall of the descending thoracic aorta in 100% of cases. In 83.3%, a right bronchial artery was related to the right first intercostal artery. Nathan and colleagues [8] first stressed this relationship. They also described the relation of the right intercostobronchial artery to the arch of the azygos vein, which functions as a landmark in preparation of the right intercostobronchial artery pedicle. This consistency made it possible to develop a technique for preparation of a left or right bronchial artery pedicle, or both. The origin and course of the bronchial arteries in the posterior mediastinum made it necessary to modify our previous excision technique to retrieve the bronchial arteries along with the lung bloc.

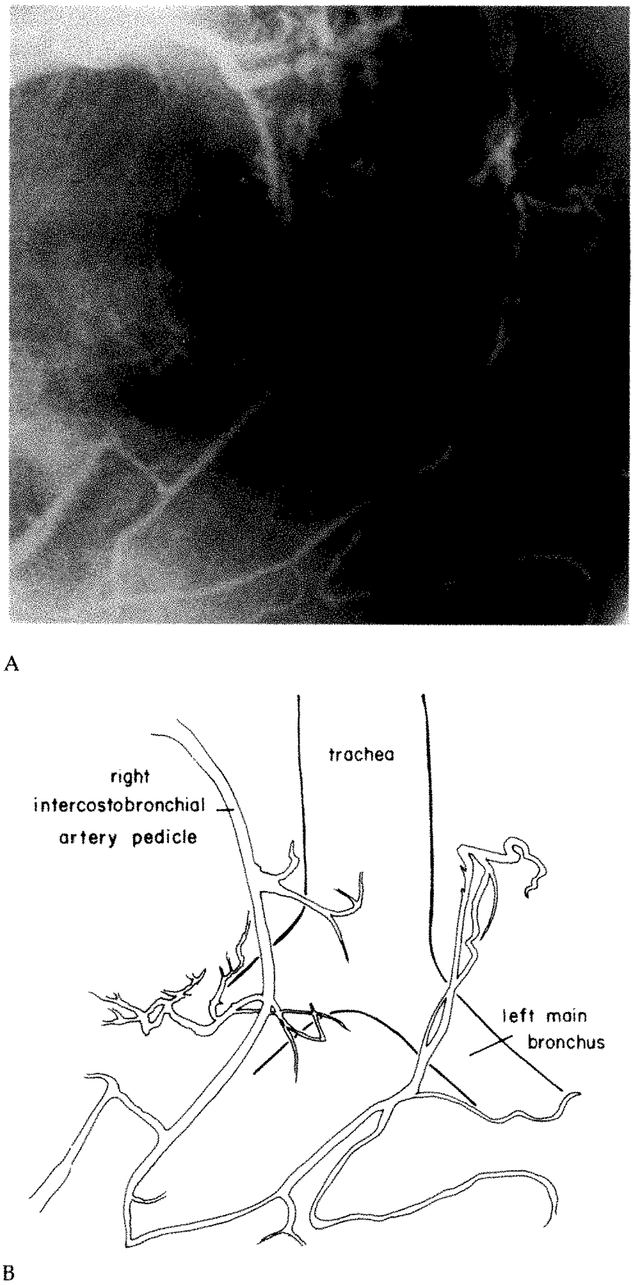

Fig 9. Angiographic study of a prepared right intercostobronchial artery pedicle (A) and line drawing of injected arteries (B). The right intercostobronchial artery supplies the distal trachea, carina, right main bronchus, and, by collaterals, the left main bronchus.

Metras [10], in 1950, was first to restore bronchial circulation successfully in animals by direct revascularization of the bronchial arteries. He reported direct revascularization of the bronchial artery circulation in 5 dogs without commenting on its effect. Canine anatomy of the bronchial arteries differs considerably from human anatomy. In dogs, the left and right bronchial arteries usually arise with one of the four cranial right intercostal arteries [11]. In 1964, Nettleblad and co-workers [12] successfully revascularized the bronchial artery in canine left lower lobe transplantation. Mills and co-workers [13] demonstrated in canine left lung allotransplantation the technical feasibility of repeatedly isolating the left bronchial artery and reconstituting the bronchial arterial circulation. They preserved and reconstituted the bronchial artery supply to the left main bronchus in 10 canine left lung transplantations using an aortic button reimplanted in the recipient's descending thoracic aorta. A control group of 11 animals underwent the same procedure except for bronchial revascularization. Mills and co-workers [13] demonstrated patency of the bronchial artery up to 3 months postoperatively in 8 animals. In the revascularized group, only two bronchial complications occurred, one of which was associated with occlusion of the bronchial artery found at autopsy. In the group without direct bronchial revascularization, bronchial complications developed in 82% of the animals. Mills and co-workers [13] made another important observation; pneumonia developed in 50% of the animals with bronchial ulceration. Bronchial ulceration occurred twice in the revascularized group and seven times in the nonrevascularized group. Bronchial ulceration-related pneumonia occurred once in the revascularized group and five times in the nonrevascularized group. We do not know if the occurring pneumonia was primary or secondary. Mills and co-workers [13] assume that the combination of bronchial ischemia and the transplant-related interruption of the ciliary mucous transport mechanism is responsible for the significantly higher incidence of pneumonia in the nonrevascularized group. In 1978, Veith and associates [14] transplanted a canine donor left lung, in an upside-down position, into the recipient's right chest and reestablished the bronchial circulation by attaching a donor aortic button containing the preserved left bronchial artery to the recipient's right subclavian artery.

Even though the importance, repeatability, and success rate of direct revascularization of the bronchial arterial circulation were clearly demonstrated in animals, direct bronchial revascularization was generally not incorporated into clinical lung transplantation. An exception was a case reported in 1973 by Haglin and co-workers [15], who reported a direct left bronchial artery revascularization with a donor's aortic button in the recipient's descending thoracic aorta with concomitant contralateral pneumonectomy, followed by right lung transplantation without reestablishment of the right bronchial artery blood supply. The left bronchus showed normal healing, whereas the right-sided anastomosis showed necrosis at autopsy. This right lung, however, had a cold ischemic time of 11 hours, which may have influenced right bronchial healing. This attempt demonstrated normal left bronchial healing after reconstitution of left bronchial arterial circulation. Despite these encouraging reports in animal experiments and 1 human patient, efforts in bronchial healing with use of direct bronchial revascularization were abandoned. Between 1982 and 1984, we reported our experience using bronchial omentopexy in a canine model of lung transplantation [16–18]. With this technique, collateral circulation to the bronchus was established in a few days and bronchial complications were significantly less than in animals without omentopexy.

We have used the omental pedicle for all single-lung and double-lung transplantations since initiating our transplant program in 1983. Although fatal airway complications have been all but eliminated after single-lung transplantation, dehiscence and stenosis have occurred and are probably the result, at least in part, of airway ischemia. Furthermore, with double-lung transplantation, a 25% incidence of fatal airway complications has occurred, preceded by endoscopic evidence of ischemic necrosis or frank infarction of the airway [19]. The higher incidence of such problems after the double-lung procedure presumably relates to the even more tenuous retrograde bronchial artery circulation that originates from pulmonary to bronchial collaterals in the lung. Recent clinical experience with bilateral bronchial anastomosis rather than tracheal anastomosis has proved more satisfactory.

Airway complications have also been reported after heart-lung transplantation. In 33 heart-lung transplantations, Griffith and co-workers [20], in 1987, reported 7 operative deaths. Of the remaining 26 recipients, fatal tracheal dehiscence developed in 2. Hakim and associates [21], in 1988, reported one fatal tracheal dehiscence in 14 heart-lung transplantations.

The techniques we describe can be used for right-lung, left-lung, double-lung, and heart-lung transplantation. Fifteen minutes more is required during retrieval, and 30 to 60 minutes is required for preparation of the pedicle. We estimate that the first intercostobronchial artery, although present in more than 80% of patients, may be of sufficient size for use in only 50% of patients. Prompt restoration of bronchial circulation is a logical refinement of current techniques for single-lung, double-lung, and heart-lung transplantation. As the period of safe lung preservation is extended, direct restoration of the airway circulation may assume even more importance in preventing airway complications.

We especially thank Marcel Mravunac (pathologist) and Don Herzberger and Ton Hooghout (cardiologists), St. Canisius Wilhelmina Hospital, Nÿmegen, the Netherlands, with whom one of us (H.H.J.S.) performed an initial 15 anatomical studies to demonstrate the feasibility of the underlying study. We thank Dawn Schuessler for assistance with manuscript preparation, Vicki Friedman for preparation of illustrations, and Jesse Hardges for assistance with dissections.

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DISCUSSION

DR J. KENT TRINKLE (San Antonio, TX): During the 1960s and 1970s lung transplantation was rather morbid. We were plagued with failures and the lack of long-term survivors. Most of the deaths and complications were due to either dehiscence or stenosis of the bronchus. Due to Dr Cooper and his colleagues in Toronto, we have resurrected this operation. He has shown us how to make it work. We are indebted to him and Dr Schreinemakers for presenting this study, which gives us a foundation on which hopefully to build a better operation. But before we write in tablets of stone that we need to have some technique to revascularize the bronchial anastomosis, I would like to point out that perhaps the jury is still out. I would like to present the clinical data from our institution in San Antonio, where we have chosen not to use any technique to revascularize the bronchial anastomosis.

At the University of Texas Health Science Center, we have had a total of 14 patients, 7 with a single-lung transplant and 7 with either a heart-lung or double-lung transplant, so there are 14 anastomoses at risk, seven tracheal and seven bronchial. Perhaps of note, we have done single-lung transplantation in 2 patients with chronic obstructive pulmonary disease due to α_1-antitrypsin deficiency, and 2 with secondary pulmonary hypertension, diseases in which it was previously thought single-lung transplantation was contraindicated. All 4 patients are doing well. We have only had one late death in 7 patients and no early deaths. But of significance to this discussion, we have had no dehiscence and no stenosis of any of the 14 anastomoses.

Tracheobronchial healing is due to a number of factors, of which ischemia is one. Rejection, preservation technique, and surgical technique are others. We did not wrap any suture line with omentum. Our antirejection regimen consists of OKT3 and steroids in the perioperative period. Preservation of the donor lung is accomplished with administration of prostaglandin E_1 to the donor for pulmonary vasodilation and to prevent platelet sludging, cold Euro-Collins solution for pulmonoplegia, and ice saline slush topically.

With our technique, we use Prolene sutures placed around the cartilages, making an effort to telescope the anastomosis at least for one ring. We use running 4-0 Prolene suture on the posterior membranous part, and interrupted figure-of-8 suture technique. We try to keep the length of the bronchus as short as possible, and use a bronchial occluder consisting of a standard endotracheal tube with a fiberoptic bronchoscopy adapter and a Fogarty catheter with a 2.5-mL saline-filled balloon. We simply place the endotracheal tube, slip the Fogarty catheter in when we do the pneumonectomy, position the balloon in the main bronchus, and inflate it. After trying dozens of different ways, we have found that this is the only one that works.

Once again I would like to express my admiration for this very meticulous study. It is essential information. I do not know if revascularization of the bronchial anastomosis is going to be necessary or not. We do not know the best way to do this operation yet; the jury is still out. With every case we are plowing new ground. We need to keep accumulating this type of information, and hopefully someday we will get the operation finetuned.

DR GERHARD ZIEMER (Hannover, West Germany): When Joachim Schaefers, currently chief resident in vascular surgery at our department, came back from a Toronto Lung Transplant Fellowship last year, he told us that he had done identical work at Toronto at that time. Although our overall single-lung transplantation experience in Hannover is limited to 4 patients so far, we consequently revascularized the bronchial arteries in our last 2 cases of single left lung transplantation.

Just recently, however, experimental work at Kyoto University in Japan came to our attention through Dr Hoki, who is in Hannover as a fellow right now. They measured posttransplantation bronchial mucosal blood flow in dogs at different bronchial sites using laser Doppler. The conclusion was that bronchial mucosal blood flow is strongly correlated with the absence of rejection, revealing a 30% drop in all transplant cases on the first postoperative day.

The consequent theory now could be that regardless of additional direct bronchial revascularization, the fate of the anastomosis is strongly linked to the immune reaction of the recipient and its microvascular consequences. Could you please comment on this statement?

DR FRANCIS ROBICSEK (Charlotte, NC): Coming home from one of the beautiful seminars of Joel Cooper from Toronto, I told myself that it makes as much sense to transplant lungs without bronchial arteries as to transplant hearts without coronary arteries. I went down to our research lab and did about a few dozen transplants with the bronchial arteries anastomosed with such "buttons," when my resident found an article by Noel Mills who already did everything in 1972 that we were doing in 1984. I would like to ask the presenters how this method differs from Noel Mills' animal experiments published in 1972.

DR HILLEL LAKS (Los Angeles, CA): I'd like to congratulate Dr Schreinemakers, Dr Cooper, and their associates for their studies of an innovative technique.

We also believe that the blood supply to the trachea is important, particularly in double-lung transplants. We have developed a technique of preserving bronchial blood supply that we believe might be more clinically applicable. It involves harvesting a segment of aorta from just proximal to the left subclavian artery to a point just below the hilum of the lung and then slipping out the esophagus, leaving all the adventitial tissue with its bronchial vessels intact. This allows one to then transplant this segment of aorta with the lung bloc and to perform an anastomosis between the donor and recipient subclavian arteries. This is very easy to do in the upper left chest.

We have shown in pigs that with methylene blue you get flushing of the mucosa all the way to the top of the trachea from this segment of aorta, and with radiopaque contrast media one can show the bronchial arteries supplying the trachea and also bronchial collateral flow all the way out to the pleural surface of both lungs. We have now applied this technique in baboons undergoing double-lung transplantation, and we have 1 long-term survivor so far. We would expect that this technique could also be clinically applicable to left and right lung isolated transplants.

DR COOPER: Dr Trinkle raises the important question as to whether it is really necessary to revascularize the airway, and to be perfectly honest, I am not sure of the answer. The vast majority of single-lung transplants have satisfactory bronchial healing these days. I am sure that when the bronchus does not heal primarily the omentum can be lifesaving.

The question is whether the omentum contributes anything to the vast majority of single-lung transplants which do heal quite well, and I do not honestly know the answer to that question. I suspect, as Dr Ziemer has suggested, that part of the answer depends on what happens to the lung in terms of rejection and infection. I think that the omentum was a relatively simple way to try and solve the problem and to protect the anastomosis. Fortunately, many centers are now becoming involved and we are in fact seeing other ways of doing things.

Perhaps Dr Ziemer was not aware of it, but Dr Schaefers did work with us in Toronto as we began developing this technique, which really was carried on primarily by Dr Schreinemakers in St. Louis, so Dr Schaefers has been aware of this work and we have communicated this method.

Dr Robicsek pointed out that one should, of course, restore bronchial circulation with lung transplantation just as one does the coronary arteries with the heart. It may seem absurd to suggest otherwise, and it is remarkable that if you go back and look at the original work of Dr Metras (the father of Dominic Metras now in Marseilles) in 1948, he did the original lung transplants in dogs and restored bronchial circulation using a button of the aorta and the left bronchial artery.

Noel Mills wrote a paper that we have quoted often. If you go back and read his paper of 1972, he very clearly showed the obvious: when he restored bronchial circulation in a series of animal experiments, bronchial healing was far superior, and you would expect that.

The difference, by the way, between this paper and that of Dr Mills is that it has been well established that it is relatively easy to secure a left lung, the left bronchial artery, and its origin from the aorta for reimplantation. This presentation was to demonstrate that for the double-lung transplant a pedicle long enough to implant into the aorta, and which would revascularize both main bronchi and the trachea, could be produced, just as Dr Mills and others have produced this for the single-lung transplant procedure.

I think this paper has the somewhat dubious distinction of being at once both out of date and ahead of its time. I think it is out of date because in looking for solutions for the ischemic tracheal problem with double-lung transplantation, the double bronchial anastomosis has come forward this last year. In Marseilles I understand they have performed six operations for cystic fibrosis with a double-lung bronchial technique without the use of omentum and have achieved excellent bronchial healing.

We have had limited experience with the same good results, as have others. So at the moment, I think the technique presented today is probably more cumbersome than what we would want to use for a double-lung transplant when the double bronchial technique will suffice.

I think it is ahead of its time because, as we extend preservation time to 12 or 24 hours, I believe that the need to restore bronchial circulation will become more critical, but we will also have the time to apply these techniques. I think Dr Laks' suggestion of keeping the whole segment of aorta and a piece of the subclavian artery is just one of the innovations that, I hope, will make restoration of bronchial circulation a routine part of single-lung, double-lung, and heart-lung transplantation.

Reduced-Size Lung Transplantation in Neonatal Swine: Technique and Short-Term Physiological Response

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Lung transplantation is now a clinical reality in adults but is limited by the scarcity of appropriate donors. The donor shortage is even more acute for neonatal and pediatric patients. Reduced-size lung grafts would expand the pool of appropriate cadaveric donors and allow HLA-matched living related lobar or segmental lung transplants. To evaluate this experimentally, we developed a model of pulmonary lobar transplantation in neonatal pigs and studied the acute hemodynamic response after transplanting the left lower lobe from a more mature donor to a neonatal recipient. Technical considerations included using the recipient atrial appendage for the pulmonary venous anastomosis. Nine pairs of pigs underwent left lateral thoracotomy. The recipient left atrial and pulmonary arterial pressures, cardiac output, and pulmonary vascular resistance were measured before pneumonectomy and after left lower lobe transplantation. Although the left atrial and pulmonary arterial pressures remained unchanged after transplantation, there was a 15% increase in pulmonary vascular resistance and a 23% reduction in cardiac output. Neither change was statistically significant. The distribution of blood flow through the left and right pulmonary arteries was unchanged after transplantation. We conclude that lobar transplantation is technically feasible in immature animals and that the pulmonary venous anastomosis to the left atrial appendage facilitates the procedure. This model may prove useful in studying lung transplantation in immature recipients and expedite implementation of reduced-size lung transplantation in neonatal and pediatric patients.

(Ann Thorac Surg 1990;49:55–60)

In recent years lung transplantation has become a clinical reality in adults due to advances in immunosuppression, improved bronchoplastic techniques, and strict patient selection criteria [1]. However, organ availability remains a major obstacle to the widespread implementation of this lifesaving procedure. As many as 87% of patients accepted for lung transplantation die waiting for a suitable donor [2]. The shortage of appropriate donor organs is particularly severe in the pediatric population. Due to the scarcity of pediatric organ donors and the serious problem of donor and recipient size disparity, no attempt has been made to perform lung transplantation in neonatal or pediatric patients. In addition, there has been little experimental work using neonatal or immature animal models to assess the clinical applicability of pediatric lung transplantation.

The severity of pulmonary hypoplasia is the most important determinant of survival among neonates with congenital diaphragmatic hernia (CDH). The respiratory difficulties are severe and, in the high-risk population, are associated with an 80% mortality [3, 4]. Although extracorporeal membrane oxygenation has been a major advance in the treatment of respiratory insufficiency in neonates, many babies with CDH are not candidates due to the severity of their pulmonary hypoplasia [5]. Transplantation of a reduced-size lung (lobe or segment) for severe pulmonary hypoplasia offers a new therapeutic approach for infants who are otherwise doomed. Extracorporeal membrane oxygenation could provide temporary neonatal cardiopulmonary support to permit time until donor lung tissue can be obtained and transplanted.

Use of a pulmonary lobe instead of the entire lung for neonatal transplantation has considerable clinical appeal because it would help solve the donor shortage problem, ameliorate the issue of size disparity, and allow living related donor transplantation with its potential immunological advantages. To evaluate the possibility of transplanting a pulmonary lobe from a more mature donor to a neonatal recipient, we developed an experimental model in neonatal swine.

Material and Methods

Eighteen York-Hampshire pigs were obtained from Pork Power (Tracey, CA). Donor pigs weighed 20 kg and were aged approximately 2½ to 3 months. Recipient pigs weighed 6 to 8 kg and were aged ten to 21 days. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for

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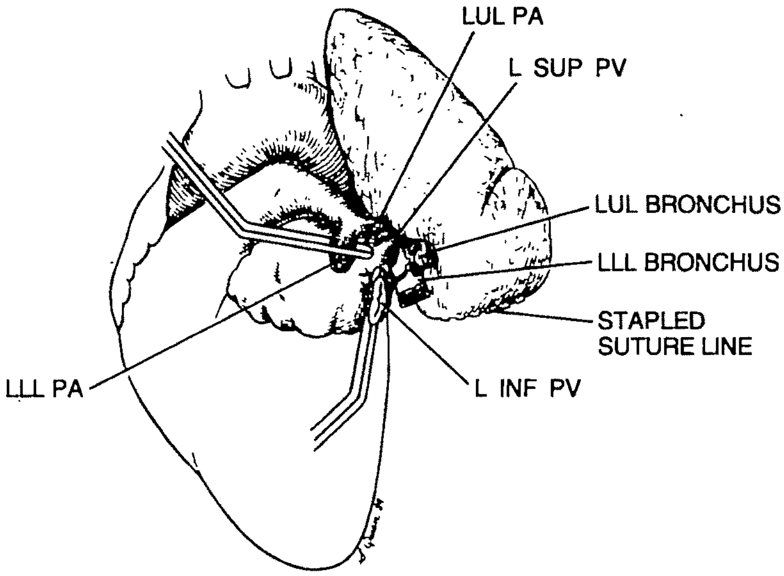

Fig 1. Donor as seen through a left thoracotomy incision after removal of left lower pulmonary lobe. Vascular clamps occlude the left lower lobe pulmonary artery and the cuff of atrium at the previous insertion of the left inferior pulmonary vein. The left lower lobe bronchus has been stapled closed. The incomplete fissure between the left upper and lower lobes has been divided with an automatic stapling device. (L INF PV = *left inferior pulmonary vein;* LLL = *left lower lobe;* L SUP PV = *left superior pulmonary vein;* LUL = *left upper lobe;* PA = *pulmonary artery.)*

the Care and Use of Laboratory Animals" prepared by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Both donor and recipient pigs received a 0.5% to 1% halothane-oxygen mixture by inhalation through an endotracheal tube after premedication with intramuscularly administered ketamine (10 mg/kg). The carotid artery and internal jugular vein of each animal were cannulated with Tygon polyvinyl catheters (internal diameter, 0.04 cm) for arterial blood pressure monitoring, arterial blood gas sampling, and venous access. The pigs were mechanically ventilated with a Narkovet II (North American Drager, Telford, PA) animal ventilator with a tidal volume (15 mL/kg) and rate appropriate to maintain normal arterial blood gas values (Ciba-Corning, model 178 blood gas analyzer, Medfield, MA). A left lateral thoracotomy with subperiosteal resection of the fifth rib was performed in both donors and recipients. In the recipient animals, electromagnetic flow transducers (C&C Instruments, Culver City, CA) were placed around the main pulmonary artery (8 to 10 mm) and the left pulmonary artery (6 to 8 mm) for measurement of cardiac output and distribution of blood flow to the right and left lungs (Narcomatic Electromagnetic Flowmeter model RT-500, Houston, TX). Tygon polyvinyl catheters (internal diameter, 0.04 cm) were placed in the pulmonary artery and the left atrium for pressure monitoring (Micron transducer and Coulbourn amplifiers, Coulbourn Instruments, Allentown, PA). All pressures and blood flows were continuously recorded on a multichannel polygraph (Astromed model 2100, Pawtucket, RI).

Donor Operation

The left lower donor lobe can be harvested without killing the animal, consistent with our eventual goal of living related donor transplantation. The ductus arteriosus is ligated and divided, and the left pulmonary artery is isolated from surrounding structures. The large hemiazygous vein, which courses superiorly over the hilum of the left lung, is ligated and divided to facilitate exposure of the superior pulmonary vein, which is preserved. The inferior pulmonary vein is isolated intrapericardially, and the left lower lobe bronchus is isolated from the left main bronchus immediately posterior to the left pulmonary artery as it enters the lung parenchyma. The incomplete fissure between the left lower and left upper lobe is divided with a TA-90 stapling device (United States Surgical, Norwalk, CT). The donor pig is systemically anticoagulated (heparin, 1,000 U intravenously) before atraumatic vascular clamps are placed across the left pulmonary artery just distal to the takeoff of the most distal branch to the left upper lobe and across the left inferior pulmonary vein as it enters the left atrium; a small atrial cuff is preserved around the vein. The left lower lobe bronchus is stapled using a TA-30 automatic stapler (United States Surgical) immediately distal to the takeoff of the left upper lobe bronchus (Fig 1). The left lower lobe is flushed through the left lower lobe artery with heparinized saline and immediately immersed in iced saline (0°C). The donor atrium and pulmonary artery are oversewn with mattressed 5-0 Surgilene sutures. The left upper lobe is examined for air leaks, and the chest is closed.

Transplantation in the Recipient

Baseline hemodynamic values in the recipient are obtained with the left chest open after confirmation of normal pH, arterial carbon dioxide tension, and arterial oxygen tension. A left pneumonectomy is then performed on the recipient. The pig is systemically anticoagulated (heparin, 1,000 U intravenously), and the left pulmonary artery is clamped at its takeoff from the main pulmonary artery. The pulmonary veins are ligated and divided extrapericardially. The left main bronchus is stapled with a TA-30 stapling device (United States Surgical) as distal as possible to preserve bronchial blood supply; the lung is then removed.

Our model of transplantation of the pulmonary lobe is similar to previous descriptions of whole lung [6–8] and adult lobar [9–12] transplantation, with the notable exception of the pulmonary venous anastomosis (Fig 2). Because the venosus portion of the atrium of animal and human neonates is very small, clamping the atrium can result in hemodynamic compromise, necessitating cardiopulmonary bypass. In addition, little recipient tissue is available for sewing the atrial patch of the donor lobe. To obviate these problems, we used an anastomosis to the left atrial appendage because it is technically straightforward and did not result in hemodynamic compromise. In addition, anastomosis to the recipient atrial appendage results in a tripod configuration of the arterial, venous, and bronchial anastomoses, which prevents torsion of the graft. The donor atrial patch is anastomosed to the recipient atrial appendage using an everting mattress technique with 5-0 PDS suture (Ethicon, Somerville, NJ). The atrial clamp is then removed to allow backbleeding through the graft, which usually takes several minutes. The pulmonary artery anastomosis is accomplished by spatulating the donor and recipient arteries as described by Veith and Richards [12]. Backbleeding from the lung is usually evident by the time the arterial anastomosis is completed with 5-0 PDS suture. The proximal clamp is released to test the adequacy of the arterial anastomosis but is reapplied to prevent a large left-to-right shunt until the bronchial anastomosis is completed and the graft can be ventilated. Last, the left lower lobe bronchus is anastomosed to the left main bronchus using a running 5-0 PDS suture. The lobar graft may then be sculpted to fit the neonatal thorax with an automatic stapling device.

Experimental Protocol

Baseline hemodynamic values, including left atrial and pulmonary arterial pressures and cardiac output, are obtained in the recipient pig before transplantation. Pulmonary vascular resistance (PVR) is calculated using the following formula:

$$\text{PVR (dynes} \cdot \text{s} \cdot \text{cm}^{-5}) = \text{pulmonary artery pressure (mm Hg)} - \text{left atrial pressure (mm Hg)/cardiac output (mL/s)} \times 1332.$$

After left pneumonectomy, the left lower lobe is transplanted. After clamps are removed and both blood flow and ventilation have been restored to the graft, adequacy of ventilation is determined by blood gas analysis of samples taken from the donor pulmonary vein. Recipient pigs were allowed a 30- to 60-minute period to stabilize after transplantation. Between one and four hours after transplantation, hemodynamic variables were measured. In 4 transplant recipients, blood from the right inferior pulmonary vein (native right lung) and the left inferior pulmonary vein (lobar graft) were sampled for blood gas analysis. The animals were killed at the end of the study period.

Data were analyzed by paired Student's t test.

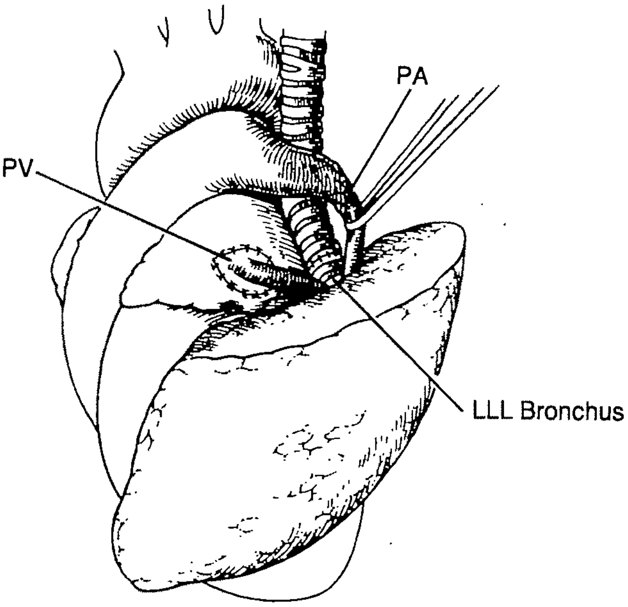

Fig 2. Recipient heart after transplantation (left lateral view). The left pulmonary artery (PA) is retracted to visualize the anastomosis of the left lower lobe (LLL) bronchus to the left main bronchus. The left inferior pulmonary vein (PV) with its atrial cuff is anastomosed to the recipient left atrial appendage.

Table 1. Pretransplant and Posttransplant Hemodynamic Data[a]

Variable	Pretransplant	Posttransplant
Mean PA (mm Hg)	14 ± 4	16 ± 3.5
LA (mm Hg)	5 ± 2	6 ± 3
Cardiac output (mL/min)	1,149 ± 296	888 ± 165
PVR (dynes · s · cm^{-5})	647 ± 341	744 ± 351

[a] Values are mean ± standard deviation.

LA = left atrial pressure; PA = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

Results

Seven of the nine pairs of pigs survived the entire experimental protocol. Two recipients were excluded from the analysis. The first excluded recipient thrombosed the pulmonary venous anastomosis, resulting in extremely high pulmonary arterial pressures and PVR. This was our first attempt at lobar transplantation, and an everting mattress technique was not used for the pulmonary venous anastomosis. Use of the everting mattress anastomotic technique in subsequent transplants prevented this complication. The second excluded immature pig died as a result of anesthetic complications before the transplant was completed. Harvest of the left lower lobe is technically straightforward; the donor animal need not be killed. The donor lobe remained in cold immersion for 40 to 120 minutes before transplantation. Similarly, left lower lobe transplantation in the more immature recipient was technically feasible and was facilitated by using the left atrial appendage for the pulmonary venous anastomosis.

Hemodynamic data are presented in Table 1. Pressures in both the pulmonary artery and the left atrium remained essentially unchanged after transplantation. Pulmonary vascular resistance increased 15% after transplantation. The distribution of cardiac output before transplantation

Table 2. Pulmonary Venous Blood Gas Analysis Data After Transplantation[a]

Variable	Right Lung	LLL Transplant
pH	7.42 ± 0.04	7.69 ± 0.09[b]
$PvCO_2$ (mm Hg)	36 ± 6	15.6 ± 6[c]
PvO_2 (mm Hg)	281 ± 164	410 ± 23

[a] Data are mean ± standard deviation. [b] $p < 0.03$ as compared with the blood pH of the right inferior pulmonary vein. [c] $p < 0.004$ as compared with the right inferior pulmonary venous $PvCO_2$.

LLL = left lower lobe; $PvCO_2$ = partial pressure of carbon dioxide in blood sampled from the inferior pulmonary vein from the right lung or the LLL graft; PvO_2 = partial pressure of oxygen in blood sampled from the inferior pulmonary vein from the right lung or the LLL graft.

was 41% and 59% to the left and right lungs, respectively. Although there was a 23% decrease in recipient cardiac output after transplantation, from 1,149 to 888 mL/min, the distribution of blood flow to the left and right pulmonary arteries was unchanged after transplantation. Neither the increase in PVR nor the decrease in cardiac output was statistically significant ($p = 0.3$).

The blood gas analysis data are presented in Table 2. The lobar graft appeared to induce a significant respiratory alkalosis and hypocapnea as compared with the native right lung. The pH and venous carbon dioxide tension of blood exiting the lobar graft was significantly different from that of the blood exiting the native right lung ($p < 0.03$ and $p < 0.004$, respectively).

Comment

Harvesting a lobar graft from a more mature donor and transplantation into a neonatal swine recipient is technically feasible and physiologically sound. The larger size of the left lower lobe provides sufficient tissue to allow distensible venous and arterial anastomoses, preventing fixed PVR [11]. The size discrepancy between the donor and recipient bronchus is easily managed by anastomosis of the left lower lobe bronchus to the recipient left main bronchus. The small size of the recipient left atrium, however, makes a standard anastomosis of the donor pulmonary vein to the venous portion of the atrium technically very difficult and potentially would result in hemodynamic compromise if a sidebiting clamp was applied to the atrium. Use of the recipient left atrial appendage is technically far easier and is well tolerated hemodynamically. In addition, anastomosis of the pulmonary vein to the atrial appendage result in a tripod configuration of the three anastomoses. This configuration prevents torsion of the graft, which is a greater concern in lobar transplantation than it is in whole lung transplantation.

All previous studies of the immediate hemodynamic response to single-lung or lobar transplantation have been performed in adult animals and have focused on problems of denervation and a limited ability to modulate PVR, resulting in elevated PVR after transplantation [9, 13, 14]. In our neonatal model, the more mature lobar graft readily accommodated the blood flow from the neonatal recipient despite denervation; as a result, there was no increase in pulmonary arterial pressure and only a slight increase in PVR. An additional determinant of the mildly increased PVR was the 23% decrease in cardiac output after transplantation. Preservation of the distribution of blood flow through the right and left pulmonary arteries after transplantation suggests that generalized myocardial depression rather than unilaterally increased resistance in the transplanted lobar graft was the cause of the decreased cardiac output. Although the cause of the reduced cardiac output probably is multifactorial, anesthetic myocardial depression and long duration of the procedure are likely contributors. The greater proportion of blood flow to the right lung (59%) was observed both preoperatively and postoperatively. This phenomenon likely reflects the effect of the right lateral decubitus position on blood flow distribution or the normally greater blood flow to the right lung as observed in dogs [15].

Although the more mature lobar graft in this model functioned well in the face of normal PVR and compliance in the contralateral native lung, it is unknown whether the transplanted lobe could accommodate the increased blood flow and preferential ventilation required under conditions simulating congenital diaphragmatic hernia. The high PVR and very poor compliance observed in CDH are analogous to conditions observed in pulmonary fibrosis, the leading current indication for single-lung transplantation in adults [1]. We are currently studying this issue in experiments that closely simulate the hemodynamic conditions of CDH.

Single-lung transplantation in adults was first attempted by Hardy and co-workers in 1963 [16]. Over the next two decades, 37 more attempts at single-lung transplantation were made worldwide. Only 2 patients left the hospital; they survived for 6 and 10 months. The rest died of graft failure, bronchial dehiscence, or rejection in the early postoperative period [17]. Cooper and colleagues [1] recently reported remarkable success in a series of 11 patients, with 8 (73%) surviving during the 4-month to 4-year posttransplant follow-up. These more encouraging results were the result of multiple factors, including advances in management of immunosuppression of lung transplant recipients, especially the introduction of cyclosporin A. In addition, recognition of the deleterious effects of corticosteroids on bronchial healing [1] and use of omentum [18] to protect and revascularize the bronchial anastomosis have greatly reduced bronchial complications. Despite these encouraging results, serious obstacles remain to the widespread implementation of lung transplantation for end-stage lung disease.

The supply of donor lungs is far more limited than that of any other transplant organ [19]. Veith [2] reported that 49 of 56 patients accepted for lung transplantation died while waiting for a suitable donor. The sensitivity of the lung to ischemic injury and the lack of adequate methods of prolonged lung preservation limits the donor procurement pool. In addition, common problems of organ donors such as pneumonia, pulmonary edema, and thoracic trauma further limit lung donor availability. Size disparity between donor and recipient also commonly prevents use of donor organs.

The shortage of donor organs is even more severe for potential pediatric lung transplant recipients. In general, size disparity is a much more common problem for pediatric recipients than for adults. Currently, infants die waiting for a donor kidney, heart, or liver of appropriate size. Accordingly, lung transplantation has never been performed in neonates or children due to the paucity of potential donors and a lack of understanding of the physiological response to transplantation in immature recipients.

Certain congenital lung lesions result in severe pulmonary hypoplasia and neonatal death. Infants with prenatally diagnosed CDH have a mortality rate of 80% [3, 4] despite maximal postnatal ventilatory care and the use of extracorporeal membrane oxygenation. The poor ventilatory compliance and elevated PVR of the remaining contralateral lung in infants with CDH would result in preferential ventilation and perfusion of the transplanted lung, as occurs in adult lung transplant recipients with pulmonary fibrosis [1]. Other possible indications for lung transplantation in the pediatric population include bronchiolitis obliterans [20], bronchopulmonary dysplasia [21], and oligohydramnios-induced pulmonary hypoplasia [22]. But the scarcity of pediatric lung donors and the problem of size disparity currently make whole-lung transplantation in neonatal and pediatric patients untenable.

Reduced-size lung transplants (lobe or segment) offer several distinct advantages. The supply of organs could be increased as the lungs of a single cadaveric donor could be divided to treat multiple lobar recipients. Use of reduced-size lung grafts, sculpted to accommodate a specific recipient, would also alleviate the problem of size disparity and further improve the efficient use of organ donors. Finally, use of lobar grafts would make possible living related transplantation, with its potential attendant immunological advantages [23].

Consideration of organ transplantation in neonates provokes many unanswered questions. Recent encouraging clinical developments in neonatal transplantation, including cardiac transplantation for hypoplastic left heart syndrome [24] and successful transplantation of segmental liver grafts from adult donors into infant recipients with biliary atresia [25], have made these questions more pressing. What constitutes optimal immunosuppression in the neonate and how is it altered by growth and development? Likewise, the effects of chronic immunosuppression on the infants' growth and development constitute a major unresolved issue. The growth potential of a denervated mature lobar graft in a neonate is another uncharted area. Finally, the recovery potential of the contralateral hypoplastic lung in babies with CDH after lung transplantation is an area worthy of investigation.

Lobar transplantation in neonatal and pediatric patients has many clinically relevant advantages, including eliminating the problem of size disparity, increasing the number and the efficient use of donor organs, and making possible the use of living related transplantation, with its potential attendant immunological benefits. This model may prove useful in exploring experimentally many of the issues that will facilitate implementation of reduced-size lung transplants in neonatal and pediatric patients.

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DISCUSSION

DR JOHN C. WAIN (Boston, MA): My colleagues and I have also conducted a similar series of experiments in a sheep model using the right upper lobe of adult ewes weighing 50 to 60 kg and transplanting it in place of the left lung in a lamb, usually 2 to 3 weeks of age and weighing 8 to 10 kg. Our method has been a little bit different in that we were interested in the response to transplantation itself, so we have attempted survival experiments. We have found, as you have, that left atrial anastomosis is important. In all animals that had a pulmonary venous anastomosis some venous stenosis and infarction developed in the survival phase. Of 16 animals, we had two intraoperative deaths and 11 that survived. Of the latter group we had 9 (all with left atrial anastomoses) who lived longer than 24 hours, the longest survival being 3 months without immunosuppression and with a functioning lung graft.

I have two questions. In the observations of the graft response to transplantation, what was the timing of those observations in relation to the timing of the transplantation? Are any of the responses related to your ischemic interval, which was not specifically referred to here?

DR CRAIG LILLEHEI (Boston, MA): My colleagues and I certainly have been intrigued by this idea and have conducted similar experiments at the Children's Hospital in Boston. We have used a somewhat different model, that is, neonatal lambs that weighed approximately 2 to 5 kg; this is more analogous to the human situation. But as you described, we think pulmonary lobar transplantation is quite feasible. We are intrigued by the use of this in congenital diaphragmatic hernias, and certainly in the possibility of using extracorporeal membrane oxygenation as a bridge.

One of the problems that has frustrated us is that infants can be well supported on extracorporeal membrane oxygenation for a period of 2 to 3 weeks, but thereafter the support is not very good. To find a donor in that narrow window, we have been anxious to increase the donor pool. Specifically, what we have done over the last 6 months is to use lobar reduction techniques, that is, taking that lobe and trimming it down further. The idea is that this may allow us to use adult donors, either cadavaric or living related, for human neonates.

DR CROMBLEHOLME: Dr Lillehei, your points are very well taken. Dr Wain, in the chronic preparations that I mentioned, we have begun sculpting them down to fit. The chest of a neonatal pig is actually very narrow, and we have sculpted the transplants using automatic stapling devices. We are just in the process of getting into the anatomy lab and trying to sort out what would be the best approach to use for human transplantation. One approach using an adult donor (either cadaveric or, down the road, a living relative) is using the superior segment of the left lower lobe, which 75% of the time has a single artery, a single vein, and a proper sized bronchus. If we wanted to stick to anatomical segments, that might be a viable alternative. But as you point out, it may not be necessary to stick to anatomical lines. You could sculpt the lobe to suit the size of the recipient.

Infusion of Nifedipine After Coronary Artery Bypass Grafting Decreases the Incidence of Early Postoperative Myocardial Ischemia

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We performed a randomized study on patients undergoing elective coronary bypass grafting to examine whether postoperative infusion of nifedipine (n = 25) could reduce the incidence of isolated transient myocardial ischemia, myocardial infarction, or both. The control group (n = 25) received nitroglycerin. Hemodynamic and Holter monitoring and serial assessment of enzymatic and electrocardiographic changes were performed for all patients. Both groups showed comparable preoperative and operative data. The incidence of myocardial infarction was significantly lower in the nifedipine group (n = 1) as compared with the control group (n = 4), whereas the number of patients with isolated transient myocardial ischemia was similar in both groups (nifedipine, 3; control, 4). At the time of peak activity, levels of creatine kinase (350 ± 129 versus 511 ± 287 IU/mL), creatine kinase-MB (8.4 ± 5.4 versus 17.1 ± 11.0 IU/mL), and glutamate-oxaloacetate-transaminase (30.4 ± 4.4 versus 41.0 ± 7.9 IU/mL) were markedly lower in the nifedipine group ($p < 0.05$).We conclude that infusion of nifedipine after elective coronary artery bypass grafting effectively decreases the incidence of myocardial infarction and the extent of myocardial necrosis during the early postoperative period.

(Ann Thorac Surg 1990;49:61–8)

Coronary artery bypass grafting (CABG) is the most commonly performed procedure in cardiac surgery, providing us with an increasing amount of data and knowledge relating to application, technique, and postoperative management. In spite of this, the incidence of the most serious complication of bypass procedures with the exception of mortality, perioperative myocardial infarction (MI), is still between 2% and 20%, depending on patient selection and applied diagnostic criteria [1–9]. Because the quality of surgical technique and postoperative care have already reached a high standard, additional therapeutic measures that may decrease the incidence of this complication are required.

In an effort to decrease the incidence of postoperative myocardial ischemia, pharmacological interventions during the early postoperative period may be valuable. The slow channel calcium blocker nifedipine has been shown to exert profound antiischemic effects under different clinical and experimental conditions, mainly by increasing the oxygen supply of the myocardium [10–14]. Because a decrease in flow resistance distal to anastomoses or in borderline perfused coronary arteries may help to prevent severe ischemia, we investigated the antiischemic efficacy of continuous postoperative infusion of nifedipine in a randomized study performed in patients undergoing elective coronary bypass procedures. To evaluate the occurrence of myocardial ischemia, Holter monitoring and serial assessment of changes in electrocardiogram (ECG) and enzyme activity were performed.

Material and Methods

The study involved 50 patients undergoing elective CABG. Patients with previous CABG, unstable angina, additional surgical procedures, or need of rethoracotomy due to excessive postoperative bleeding were excluded from the study. The patients were randomly assigned to control (n = 25) and treatment (nifedipine, n = 25) groups. Informed consent was obtained from each patient. Patients received the last medications (nitrates, β-blockers or calcium antagonists) on the evening before operation.

All patients were premedicated with flunitrazepam (2 mg orally) about one hour before arrival in the operating room. After preoxygenation, anesthesia was induced with etomidate (0.2 to 0.3 mg/kg), fentanyl (0.005 to 0.007 mg/kg), and diazepam (0.1 to 0.3 mg/kg). Intubation was performed after administration of pancuronium (0.1 mg/kg). The patient's lungs were ventilated with a rate of 12 breaths per minute and a tidal volume of 10 to 12 mL/kg. Anesthesia was maintained with O_2/N_2O, fentanyl, diazepam, and pancuronium.

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For myocardial protection during ischemia, patients received an average of 1,220 ± 280 mL St. Thomas' Hospital cardioplegic solution through the aortic root in addition to systemic hypothermia (29°C rectal temperature) and topical cooling.

Patients assigned to the nifedipine group had continuous nifedipine infusion (minimum dose, 10 μg/kg/min) from two hours until 24 hours after aortic cross-clamp time (ACCT). During the same period, patients assigned to the control group had continuous nitroglycerin infusion (minimum dose, 1 μg/kg/min). The infusion rate was increased in both groups to manage postoperative hypertension (greater than 90 mm Hg mean arterial pressure) if necessary. Plasma levels of nifedipine were assessed at 12 hours after onset and immediately before the end of nifedipine infusion. In all nifedipine-treated patients, the plasma levels were above the minimum therapeutic level of 10 ng/mL (range, 13 to 29 ng/mL). There was no case of nifedipine-induced severe hypotension.

Hemodynamic Measurements

All patients had arterial (through a radial artery cannula) and left atrial (catheter inserted during operation) pressure monitoring. Preoperatively, a Swan-Ganz catheter was inserted percutaneously into the pulmonary artery through the jugular vein to assess pulmonary artery pressure, pulmonary artery wedge pressure, cardiac output (Edwards 9520A thermodilution computer), and central venous pressure. From these data, pulmonary artery resistance and cardiac index were calculated. An assessment of hemodynamic variables was performed immediately before operation and at 30 minutes, 1 hour, and 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after ACCT.

Holter Monitoring and Electrocardiographic Recordings

Three-channel Holter monitoring was performed postoperatively on all patients using Marquette Holter Recorders (series 8500). Monitoring was started two hours after ACCT in the intensive care unit and lasted 24 hours. To avoid contamination of the operation site, the electrodes were placed so that channels 1 through 3 approximated ECG leads V2, V5, and aVF, respectively. All tapes were evaluated by the same investigator without knowledge of the patient's group assignment for ST-segment elevations and depressions and arrhythmias on a semiautomatic basis using a Marquette Laser Holter XP device.

In addition, all patients had 12-lead ECG recordings shortly before and repeatedly for 36 hours after operation (parallel to enzymatic measurements), as well as on the tenth postoperative day. Patients with left ventricular hypertrophy, preoperative or postoperative left bundle-branch block, and right bundle-branch block were excluded from postoperative Holter and ECG analysis. The patients were classified as having either isolated transient ischemic events (ITIEs), transient coronary spasm, MI, or an uneventful postoperative course using the following criteria:

Isolated transient ischemic attacks: At least one episode of horizontal or downsloping ST-segment depression ≥1 minute of ≥ 1 mm measured 60 to 80 ms from the J point in at least one channel with no signs of evolving myocardial infarction.

Transient coronary spasm: Transient monophasic ST elevation without a Q wave in respective leads and a shift of the ST-segment/R-wave ratio toward higher ST segments. If ST-segment elevations did not match these criteria or those for MI, other causes, such as postoperative pericarditis, were assumed.

Myocardial infarction: Persistent typical ST-segment elevations of ≥2 mm, measured 60 to 80 ms from the J point in at least one channel and development of a new Q wave (lasting more than 0.04 s and more than one quarter of the following R-wave in amplitude, as defined by the American Heart Association) in the corresponding 12-lead ECG at discharge or during the 36-hour observation period after operation.

Uneventful postoperative course: No ST-segment depressions or signs of MI as defined.

Biochemical Analysis

Levels of creatine kinase (CK), the MB-isoenzyme of CK (CK-MB), lactate dehydrogenase, glutamate-oxaloacetate-transaminase, and glutamate-pyruvate-transaminase were assessed immediately before operation and at 1 hour and 2, 3, 4, 6, 8, 12, 16, 20, 24, and 36 hours after ACCT using enzymatic fluorometric methods.

Statistical Analysis

Data are presented as mean ± standard error of the mean. For statistical analysis, the raw data for each timepoint and the peak value of each variable within a patient were used. A paired *t* test was performed for comparison of groups of data. Because standard deviation differs in many variables between the groups, the unpaired version was used. Due to the skewness of some of the enzymatic data, we applied the Wilcoxon rank-sum test on each variable found to be significantly different in the *t* test. Standard χ^2 test was used for comparison of anumeric data between the two groups. For all results, the 95% and 99% confidence limit was adopted for statistical significance.

Results

Preoperative patient analysis of variables considered to be of prognostic significance for perioperative morbidity are shown for the nifedipine and control groups in Table 1. These data demonstrate the similarity of both groups with regard to the severity of coronary artery disease and functional myocardial status. In addition, evaluation of operative data revealed no significant differences between both groups for any characteristics, such as ACCT, bypass time, or number of distal anastomoses (Table 2). Early mortality (defined as any death occurring during hospitalization or within 30 days after operation) was 4% in both groups (1 patient per group). Both patients died more than ten days after operation of respiratory failure, septicemia, and subsequent multiorgan failure. In both cases, perioperative MI was ruled out during the observation period and at autopsy. The data for both patients remained in the study.

Hemodynamic Variables

Changes in hemodynamic variables over the 24-hour postoperative observation period are shown in Table 3. The preoperative hemodynamic measurements showed similar values for both groups except for a slightly lower cardiac index in the nifedipine group. The continuous infusion of nifedipine starting two hours after ACCT did not significantly change the course of mean arterial pressure, heart rate, or central venous pressure as compared with those of the control group. At 24 hours after ACCT, however, left atrial and pulmonary artery pressure were lower and cardiac index was higher in the nifedipine group than in the control group. These data indicate that nifedipine had no detectable hypotensive effect but rather induced a favorable effect on restoration of myocardial function during the 24-hour follow-up period.

Electrocardiogram and Holter Monitoring

Data from ECG and Holter monitoring are shown in Table 4. Five patients (3 in the nifedipine group and 2 in the control group) had to be excluded from the analysis either due to technical reasons or because their ECGs prevented the diagnosis of ischemia (see Material and Methods section). Enzyme levels in these patients were within the normal range except in 1 (control group: CK, 950 IU/mL; CK-MB, 30 IU/mL), and their data were included for hemodynamic and enzyme analysis. The prevalence of ITIEs was similar in the nifedipine and control groups. Transient coronary spasm was detected in only 1 patient (control group) and was not accompanied by any hemodynamic instability. Five patients (10%) had perioperative MI; 1 received nifedipine and 4 had been assigned to the control group ($p < 0.05$). The history of preoperative MI or operative data such as ACCT, bypass time, or number of distal anastomoses had no influence on the occurrence of postoperative ITIEs or MI.

Table 1. Preoperative Patient Analysis

Variable	Nifedipine	Control
No. of patients	25	25
Female	7 (28%)	5 (20%)
Male	18 (72%)	20 (80%)
Age (yr)	61.0 ± 8.1	61.5 ± 6.5
Weight (kg)	74.8 ± 8.9	77.4 ± 8.5
One-vessel disease	1 (4%)	0
Two-vessel disease	7 (28%)	7 (28%)
Three-vessel disease	17 (68%)	18 (72%)
Left main stenosis	9 (36%)	7 (28%)
Anterior/lateral MI	6 (24%)	2 (8%)
Posterior MI	9 (36%)	9 (36%)
NYHA functional class		
I or II	3 (12%)	5 (20%)
III or IV	22 (88%)	20 (80%)
Preoperative therapy		
Single drug	5 (20%)	3 (12%)
Double drug	15 (60%)	15 (60%)
Triple drug	5 (20%)	7 (28%)
Nifedipine	12 (48%)	13 (52%)

MI = myocardial infarction; NYHA = New York Heart Association.

Table 2. Operative Data

Variable	Nifedipine	Control
No. of patients	25	25
ACC time (min)	54.5 ± 19.7	58.9 ± 20.4
ACC time > 60 min	8	8
ECC time (min)	112.2 ± 29.9	119 ± 36.4
ECC time > 120 min	8	10
No. of grafts/patient	3.44 ± 0.85	3.64 ± 0.81
Two grafts/patient	3 (12%)	1 (4%)
Three grafts/patient	16 (64%)	17 (68%)
Four grafts/patient	5 (20%)	5 (20%)
Five grafts/patient	1 (4%)	1 (4%)
Six grafts/patient	0	1 (4%)
No. of IMA grafts	7 (28%)	7 (28%)
Endarterectomy	3 (12%)	2 (8%)
Mortality	1 (4%)	1 (4%)

ACC = Aortic cross-clamp; ECC = extracorporal circulation; IMA = internal mammary artery.

Myocardial Enzymes

Preoperative and postoperative serum levels of the relatively cardiospecific enzymes CK and CK-MB are shown in Figure 1. In both groups, CK and CK-MB levels increased during the first four to six hours after ACCT in comparison with preoperative values, indicating a similar extent of myocardial injury as a result of the operative procedure. However, significant differences in both enzyme levels were observed during the following period up to 36 hours after ACCT: CK levels continued to increase slightly and CK-MB levels actually decreased in the nifedipine group, whereas both enzyme levels increased markedly in the control group. In addition, peak values for CK, CK-MB, and glutamate-oxaloacetate-transaminase were significantly higher in the control group (Table 5). No differences were detected with regard to peak lactate dehydrogenase and glutamate-pyruvate-transaminase levels between both groups, indicating that any possible effects of nifedipine on the systemic release of enzymes were not responsible for the observed differences in serum CK and CK-MB levels (Table 5).

Peak CK (375.7 ± 110.7 versus 397.2 ± 225.2 IU/mL) and CK-MB (11.4 ± 5.7 versus 10.1 ± 6.7 IU/mL) levels of patients with ITIEs did not differ from those with an uneventful postoperative course, regardless of which group they had been assigned to. However, even patients classified as having an uneventful postoperative course who received nifedipine showed a tendency toward lower serum enzyme levels as opposed to those in the control group (CK; 319 ± 134 versus 503.4 ± 278.8 IU/mL; CK-MB, 8.6 ± 5.8 versus 12.2 ± 7.3 IU/mL, not significant).

In patients with perioperative MI, as diagnosed by the combined analysis of Holter and ECG recordings, serum enzyme levels were significantly ($p < 0.01$) higher than in patients with an uneventful postoperative course (CK, 640

Table 3. Hemodynamic Data

	Preoperative		1 h		2 h	
Variable	N	C	N	C	N	C
Heart rate (min^{-1})	65.4 ± 2.5	73.7 ± 3.1	86.0 ± 3.8	95.4 ± 3.0	83.4 ± 2.2	93.7 ± 2.2
Mean arterial pressure (mm Hg)	75.4 ± 1.8	78.8 ± 2.5	61.8 ± 1.9	64.2 ± 2.5	72.2 ± 2.5	79.7 ± 2.2
Pulmonary artery pressure (mm Hg)	17.1 ± 0.9	15.9 ± 0.8	14.3 ± 0.9	16.2 ± 1.1	16.2 ± 0.8	17.6 ± 0.9
Left atrial pressure (mm Hg)	—	—	9.3 ± 1.0	9.0 ± 0.7	9.4 ± 0.8	9.6 ± 0.8
Central venous pressure (mm Hg)	7.6 ± 0.6	8.2 ± 0.6	6.4 ± 0.7	7.4 ± 0.5	7.9 ± 0.7	9.6 ± 0.6
Cardiac index ($L/min/m^2$)	2.37 ± 0.11	2.76 ± 0.12^b	2.74 ± 0.15	2.99 ± 0.18	2.46 ± 0.14	2.85 ± 0.18
Pulmonary vascular resistance (U)	3.74 ± 0.27	3.67 ± 0.25	3.70 ± 0.30	3.0 ± 0.19	4.31 ± 0.30	4.12 ± 0.31

Hemodynamic variables before operation and for 24 hours after opening of the aortic cross-clamp.

[a] Value differs significantly from that for N group ($p < 0.01$). [b] Value differs significantly from that for N group ($p < 0.05$).

C = control group (n = 25); N = nifedipine-group (n = 25); U = arbitrary unit.

± 237.4 versus 397.2 ± 225.2 IU/mL; CK-MB, 34 ± 5.5 versus 10.1 ± 6.7 IU/mL). These data confirm the relatively high sensitivity of serum enzyme levels for detection of MI.

Comment

The results of this study show that continuous postoperative infusion of the calcium channel blocker nifedipine in patients undergoing elective coronary bypass procedures can be safely performed without a detectable incidence of hypotensive crisis and effectively decreases the incidence of early postoperative MI. This conclusion is based on the significantly lower serum CK and CK-MB levels as well as the lower incidence of Holter monitoring- and ECG-proven occurrence of MI during the early postoperative period in nifedipine-treated patients as opposed to a control group.

Two major variables indicate the early success rate of coronary bypass procedures: early mortality and occurrence of perioperative MI. To evaluate beneficial effects of a certain therapeutic regimen in patients undergoing CABG, reliable diagnostic criteria for defining postoperative myocardial ischemia are mandatory. Conflicting reports have been published during the last decade about the diagnostic values of different methods. Most investigators emphasize the combined use of various methods, such as the amount of enzyme release, ECG evaluation, radionucleotide methods, and functional measurements [2, 5–9]. Although ambulatory ST-segment monitoring has become an established method in the detection of ischemic episodes [15–17], it was introduced only recently as an additional noninvasive method for detection of ischemia during the early postoperative phase [18, 19]. This is probably as a result of difficulties in interpretation of ST-segment changes, known to be affected by a number of technical and clinical factors such as electrode imbalance and temperature changes or history of MI, postoperative pericarditis, vasospasm, or changes in the activity of the autonomic nervous system [16, 17].

To circumvent these problems and to increase the specificity of the interpretation of various ST-segment changes observed in Holter monitoring, we defined strict diagnostic criteria for various "types" of myocardial ischemia such as MI, ITIEs, and transient coronary spasms, based on serial 12-lead ECG recordings and Holter monitoring.

Although certain limitations exist, this combined approach offers the possibility of a more detailed analysis of ischemic events over a certain period of time. In particular, this method appears to be superior to the diagnosis of MI solely by the occurrence of new Q waves, which lacks sensitivity as well as specificity even in combination with enzyme analysis [20]. In this respect, the exact documentation of a lasting ST-segment elevation, eventually leading to development of a new Q wave, appears to be more reliable for the diagnosis of MI.

Our results show that ITIEs are common after CABG (17% overall) but are not affected by nifedipine. Because patients with documented ITIEs had similar CK and CK-MB levels in comparison with patients with uneventful postoperative course, however, the clinical significance of this variable remains unclear. Only long-time follow-up studies will show whether the occurrence of perioperative ITIEs in addition to perioperative MI can be of prognostic value for the ultimate outcome of CABG procedures. The incidence of postoperative ITIEs (17%) was lower in our study than in that recently reported by Knight and colleagues (40%). The reasons are not readily apparent but may be related to the following factors. First, continuing ST-segment elevations were not attributed to myocardial ischemia in our study because they may stem from various accountable causes unrelated to ischemia, such as vasospasm or perioperative pericarditis. In cases of prolonged ST elevations, development of a new Q wave indicated MI in our study, whereas absence of a new Q wave suggested postoperative pericarditis. Second, recording time in our study was only 24 hours compared with 48 hours in the study performed by Knight and colleagues [18].

Vasospasm in native coronary artery or vein grafts is a rare complication in the early postoperative period after CABG. Nevertheless, several cases have been reported [19, 21]. Applying strict criteria for the diagnosis of perioperative spasms to rule out conditions such as pericarditis, we could document only 1 case (control group).

Table 3. Continued

4 h		8 h		16 h		24 h	
N	C	N	C	N	C	N	C
89.4 ± 3.3	95.9 ± 3.3	91.8 ± 3.8	94.4 ± 2.9	93.7 ± 3.2	89.6 ± 2.5	90.2 ± 2.0	92.6 ± 2.0
78.9 ± 1.9	81.1 ± 2.9	75.8 ± 2.2	79.0 ± 2.1	75.8 ± 2.0	77.1 ± 1.8	75.9 ± 1.7	80.3 ± 2.1
16.7 ± 0.7	17.0 ± 0.8	16.5 ± 0.7	18.4 ± 0.8	18.0 ± 0.8	18.9 ± 0.9	16.7 ± 0.6	20.0 ± 0.9^a
8.8 ± 0.7	9.6 ± 0.7	8.6 ± 0.7	10.5 ± 0.9	8.9 ± 0.7	10.4 ± 0.9	7.4 ± 0.7	10.7 ± 0.7^a
8.4 ± 0.6	8.9 ± 0.7	8.7 ± 3.1	8.8 ± 0.5	8.8 ± 0.6	9.6 ± 0.5	8.8 ± 0.5	9.9 ± 0.6
2.29 ± 0.14	2.74 ± 0.21	2.54 ± 0.13	2.66 ± 0.13	3.01 ± 0.14	2.79 ± 0.12	3.14 ± 0.11	2.73 ± 0.12^b
4.19 ± 0.34	4.04 ± 0.41	3.96 ± 0.26	3.40 ± 0.35	3.48 ± 0.18	3.25 ± 0.26	3.62 ± 0.22	3.40 ± 0.24

The low incidence of transient spasms in our study prevents us from drawing conclusions as to whether nifedipine may have affected their occurrence.

The most interesting finding in our study was the significantly lower incidence of MI in the nifedipine group as opposed to the control group. Myocardial infarction was present in 10% of all patients (n = 5) but in only 1 patient (4%) who received nifedipine treatment (control group, 4 patients = 16%). The incidence of perioperative MI varies considerably among different studies, which illustrates the diagnostic problems involved in assessment of perioperative MI, such as conclusive interpretation of Q waves, increases of serum enzyme levels, or both. When additional diagnostic methods with presumable higher sensitivity and specificity for MI (such as radionucleotide scan with technetium 99m pyrophosphate or assessment of regional myocardial function) are applied, the incidence of perioperative MI is in the range of 12% to 20% [2, 5–9], which coincides more closely to the 16% in our control group. In addition, our data show good correlations between high CK-MB levels (and to a lesser degree, high CK levels) and the diagnosis of MI using our combined Holter-ECG technique. Even when patients with evidence of MI were excluded from analysis, there was a clear tendency of lower postoperative CK and CK-MB levels in the nifedipine group. This is difficult to explain, because the higher enzyme levels of those patients in the control group were not accompanied by any other signs of MI, such as Holter or ECG alterations. However, given the assumption that serum enzyme levels are a sensitive marker for myocardial ischemia [9] and, at least to a certain degree, reflect the amount of damaged myocardial tissue [22], these data support the well-documented anti-ischemic [10–12] and tissue-protective potency of nifedipine [23].

Various studies have dealt with the question of whether withdrawal of nifedipine can be related to a higher incidence of postoperative graft or coronary vasospasm, but no definite conclusions have been reached [19, 24]. Because we cannot rule out the possibility that perioperative MI observed in our patients was related to vasospasm, the withdrawal phenomenon may have influenced our results as well. This appears to be very unlikely, however, because 3 of the 4 patients who showed signs of perioperative MI in the control group had no preoperative therapy with a calcium antagonist. In addition, preoperative or operative variables known to be predictive for the occurrence of perioperative ischemia, such as age, sex, severity of coronary artery disease, history of myocardial infarction, ACCT, bypass time, and the number of distal anastomoses (Tables 1 and 2), did not differ between the two groups, indicating that the lower incidence of myocardial ischemia observed in our study can be related to the antiischemic efficacy of nifedipine. The intraoperative and postoperative course of hemodynamic variables such as heart rate and arterial, pulmonary, or central venous pressure was also very similar in both groups (Table 3). Thus, it is unlikely that any nifedipine-induced differences in the external workload imposed on the heart contributed to the observed beneficial effect by reducing myocardial oxygen consumption.

The antiischemic effect of nifedipine was more likely triggered by mechanisms that act directly on the coronary

Table 4. Postoperative Myocardial Ischemia

Variable	Nifedipine (n = 22)	Control (n = 23)	*p* Value
Myocardial infarction	1	4	<0.05
Isolated, transient ischemic events	3	4	NS
Transient coronary spasm	0	1	NS

NS = not significant.

Table 5. Enzyme Data

Enzyme^a	Nifedipine (n = 25)	Control (n = 25)	*p* Value
CK	350 ± 27	511 ± 57	<0.05
CK-MB	8.4 ± 1.1	17.1 ± 2.2	<0.01
GOT	30.4 ± 4.4	45.0 ± 8.4	<0.05
LDH	325 ± 20	347 ± 32	NS
GPT	15.8 ± 2.4	15.0 ± 1.7	NS

^{a} All values are the mean ± standard deviation of peak values.

CK = creatine kinase; CK-MB = MB-isoenzyme of CK; GOT = glutamate-oxaloacetate-transaminase; GPT = glutamate-pyruvate-transaminase; LDH = lactate dehydrogenase; NS = not significant.

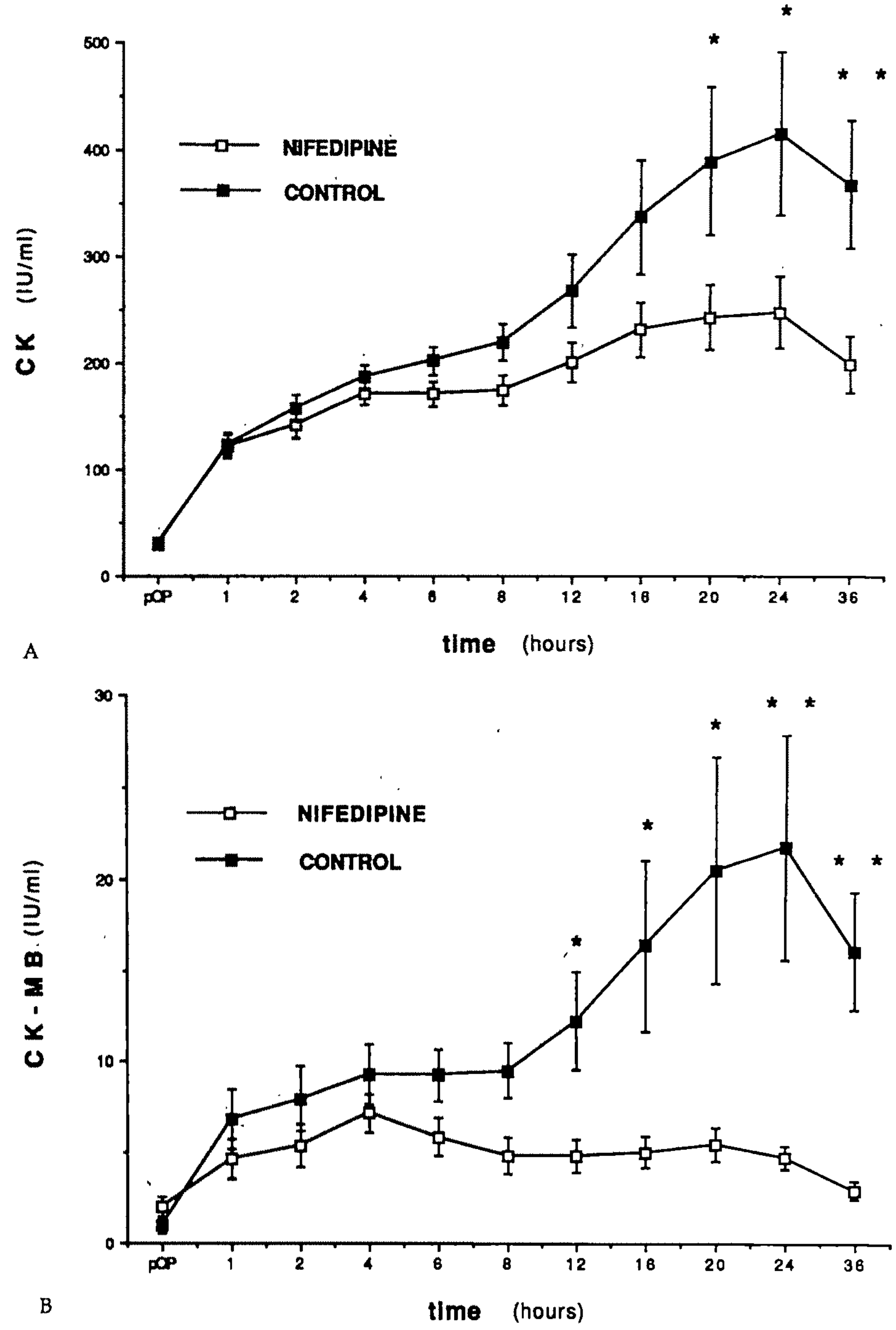

*Fig 1. (A) Serum creatine kinase (CK) and (B) MB isoenzyme of creatine kinase (CK-MB) levels before operation and for 36 hours after opening of the aortic cross-clamp. (*Value differs significantly from that for nifedipine group ($p < 0.05$); **Value differs significantly from that for nifedipine group ($p < 0.01$); IU = international units.)*

vasculature and influence myocardial blood flow in lower concentrations than are necessary to induce marked effects on systemic hemodynamic variables: nifedipine is a well-recognized drug for the treatment of angina pectoris and increases myocardial oxygen supply by dilating coronary arteries, especially in the subepicardium [12, 14]. In addition, nifedipine is a functional antagonist of α_2-receptor–mediated sympathetic coronary vasoconstriction and reduces coronary resistance by up to 30% from baseline levels [11, 12]. Hemodynamically significant α_2-receptor–mediated sympathetic coronary vasoconstriction is of special importance during various degrees of myocardial ischemia and under certain circumstances that lead to an activation of the sympathetic nervous system, such as stress, exercise, or anesthesia [11, 13, 25]. This vasodilatory efficacy of nifedipine is certainly of importance during the early postoperative period, when even a small decrease in flow resistance distal to an anastomosis or an otherwise insignificant coronary stenosis may inhibit severe myocardial ischemia and flow disturbances, which would otherwise induce clot formation and, eventually, lead to MI. Finally, it should be mentioned that nifedipine has also been reported to prolong bleeding time and significantly reduce primary and secondary platelet aggregation by inhibiting calcium transport across the cell membrane [26]. Although potentially of therapeutic significance in the prevention of ischemia after coronary bypass procedures, we cannot conclude from our data whether this reported anticoagulant property of nifedipine had any important influence on the results of our investigation. Further studies will be necessary to clarify this aspect.

In conclusion, our study provides evidence that continuous postoperative infusion of nifedipine in patients undergoing coronary bypass procedures is a potent measure in the prevention of perioperative myocardial ischemia. The infusion of nifedipine is not accompanied by any serious complications and can therefore be performed as a regular therapeutic adjunct to standard perioperative patient care.

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DISCUSSION

DR JAMES E. LOWE (Durham, NC): I am certain that all of us are grateful to Dr Seitelberger, Dr Wolner, and their colleagues from Vienna for addressing a very important clinical problem encountered by all of us involved in coronary artery bypass grafting, namely, the prevention of postoperative cardiac ischemic events. These ischemic events, even when reversible, can result in life-threatening ventricular arrhythmias and a transient decline in pump function in the early, critical postoperative period. Irreversible ischemic events eventually lead to myocardial necrosis with permanent loss of ventricular function and a subsequent decrease in functional class and long-term life expectancy after coronary bypass graft procedures.

The data presented convincingly show (1) a decrease in the incidence of new myocardial infarction in the treated group compared with controls as documented by serial postoperative electrocardiograms (4.5% in the treated group versus 17% in controls), (2) a decrease in postoperative cardiac enzyme release in the treated group compared with controls, and, perhaps most interestingly, (3) no differences in postoperative transient ischemic events between the two groups as documented by Holter monitoring.

Patients were randomly assigned to receive either nitroglycerine or nifedipine postoperatively, and the clinical characteristics of both groups are essentially identical with one potentially very important exception: 6 of 25 patients, or 24% of the nifedipine group, had had an anterior wall myocardial infarction based on the preoperative electrocardiogram, whereas only 2 of 25, or 8%, of the controls had suffered a preoperative anterior myocardial infarction. Both groups had the same incidence of preoperative inferior myocardial infarction—9 of 25 patients in each group or 36% for each group.

Therefore, based on the preoperative electrocardiograms, the patients who received nifedipine postoperatively had a threefold greater incidence of prior anterior myocardial infarction compared with controls, and both groups had the same incidence of preoperative diaphragmatic myocardial infarction. These preoperative electrographic data suggest that the patients who subsequently received postoperative nifedipine had lost more myocardium from prior preoperative myocardial infarction than control patients.

Clearly, nonviable or dead myocardium does not develop new postoperative electrocardiographic changes, does not release cardiac enzymes, and does not develop transient ST-T wave changes on Holter monitoring.

Based on these observations, I would like to ask Dr Seitelberger the following questions. (1) Could the threefold greater incidence of preoperative anterior infarction in the nifedipine patients explain all of the postoperative differences reported between groups? (2) The incidence of new postoperative Q wave infarction in the control group was 17% (4 of 23 patients). The incidence of new Q wave myocardial infarction in the literature varies greatly, but in recent years has averaged around 5% for elective patients at most centers. Isn't 17% a bit high? (3) Finally, only 7 of 25 patients, or 28% in each group received an internal mammary artery graft. Why was the internal mammary artery conduit used so infrequently?

In closing, I would like to sincerely thank Seitelberger and associates for presenting to us a very provocative report. These preliminary results are encouraging, and I hope you continue this important randomized study.

DR W. ROBIN HOWE (Paducah, KY): Unfortunately, parenteral nifedipine is not available in this country. Based on some preliminary laboratory studies a number of years back incorporating nifedipine in cardioplegia solution, I took up a simple country solution 5 years ago and began giving all patients 10 mg of sublingual nifedipine just before initiating cardiopulmonary bypass. I am glad to see there is now at least some scientific evidence supporting my impression that this has reduced perioperative ischemia.

As one measure, in our series only 2.3% of the last 1,500 patients have required any inotropic support coming off of cardiopulmonary bypass. In addition, I have never seen the reported phenomenon of internal mammary artery spasm that is certainly well described in the literature. I have three questions. (1) Would you comment on the debate about the effectiveness and bioavailability of sublingual nifedipine? (2) Why did you choose 24 hours of perfusion after operation? (3) Have you had any increased incidence of need for Neo-Synephrine (phenylephrine) because of the vasodilator effect of this drug?

DR RICHARD D. WEISEL (Toronto, Ont): I compliment Seitelberger and associates on an excellent presentation. Clinical studies such as these are required in order to improve our techniques of surgery.

My colleagues and I have also carefully evaluated postoperative metabolism looking for transient evidence of ventricular ischemia. We use oxygen consumption and lactate utilization. We have found that postoperative hypertension is one of the major stresses that does produce at least transient ischemia in the early postoperative period.

We therefore use intravenous nifedipine to eliminate the postoperative hypertension, and we have found it to be very successful. To do that, though, we had to titrate the dose. The dose that you used in Vienna was obviously too small because transient hypertension did occur in your patients. If you titrate the dose, you can prevent that from occurring, and we did find beneficial effects of the nifedipine.

We carefully looked at ventricular function and found no major depression in ventricular function associated with the hypertension. The use of a calcium antagonist, diltiazem, produced a major decrease in ventricular function at the same dosage but did improve metabolism; the ventricular function, however, was disturbing.

Therefore, more recently we have used esmolol as an intravenous infusion and found this to be very effective both in reducing function slightly and improving metabolism and preventing the postoperative hypertension and tachycardia. Therefore, we would probably recommend the combination of nifedipine and esmolol. Dr. Seitelberger, do you have any comments on this?

DR SEITELBERGER: First, Dr Lowe, as far as the relatively high incidence of preoperative myocardial infarction of 17% in the control group is concerned, I think the point is that with the Holter monitoring, we did actually detect perioperative myocardial infarctions that would have otherwise probably not been detected. If you ask the cardiologists, they can give you a hundred reasons why a new Q wave is not a new Q wave if you do not see ST segment elevations before that. And if you look at our enzyme data, the interesting thing is that we had no patients with CK-MB levels higher than 40 U/L, which actually indicated that the infarcts we saw were pretty small in size and may probably have not been detected with a routine procedure. I think this is one of the reasons why our infarct incidence in the control group is higher than in the literature.

As far as the high incidence of arterial wall infarction is concerned, the overall number of infarctions was similar in both groups. With the Holter method you can actually even see the changes in the ST segment elevations in the border zones of previously infarcted areas, so I don't really think the high incidence of arterial wall infarction had a significant effect on the results of our study.

We used few mammary artery grafts because this was just the politics of our department at that time. The study is now over, and we have increased the incidence of mammary artery grafts to 80% of our patients.

Dr Howe, we used a nifedipine infusion because we really wanted to make sure that nifedipine was having its effect all the time. As long as the patients are intubated and all sort of things are going on in the intensive care unit, we really could not guarantee that nifedipine would be effective if we just applied it sublingually. Maybe there would have been the same results.

The interesting thing is—and I think this answer goes to both of the two last discussants—we did not use any catecholamines in this study. Our dose of nifedipine was relatively low, and there is clinical and experimental evidence that you can achieve an effect of nifedipine on the coronary arteries before you actually see peripheral vascular effects. We could actually choose a very low nifedipine dose to start off, but we did increase the dose if we had to manage hypertensive crises. The doses I showed were just the minimal doses we infused; they are not the doses that we used for all patients.

Primary Tracheal Tumors: Treatment and Results

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One hundred ninety-eight patients with primary tracheal tumors were evaluated in 26 years. One hundred forty-seven tumors were excised (74%): 132 (66%) by resection and primary reconstruction, seven by laryngotracheal resection or cervicomediastinal exenteration, and eight by staged procedures. Eleven more were explored. Forty-four squamous cell carcinomas were resected, 60 adenoid cystic, and 43 assorted tumors, benign and malignant. Eighty-two patients underwent tracheal resection with primary reconstruction, and 50 had carinal resection and reconstruction. Surgical mortality for resection with primary reconstruction was 5%, with one death after tracheal and six after carinal repair. Six patients had stenosis after tracheal or carinal resection; all underwent reresection successfully. Nearly all patients with squamous or adenoid cystic carcinoma were irradiated postoperatively. Twenty of 41 survivors of resection of squamous cell carcinoma are living free of disease (some for more than 25 years), 39 of 52 with adenoid cystic carcinoma (up to nearly 19 years), and 35 of 42 with other lesions (5 lost to follow-up). Comparison of length of survival of patients with squamous cell carcinoma and adenoid cystic carcinoma who are alive without disease with those who died with carcinoma supports surgical treatment (usually followed by irradiation). Positive lymph nodes or invasive disease at resection margins appear to have an adverse effect on cure of squamous cell carcinoma; such an effect is not demonstrable with adenoid cystic carcinoma.

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In large part because of the rarity of primary tracheal tumors, few large clinical series have been reported reflecting application of contemporary techniques of tracheal resection with primary reconstruction. Notable among these are reports from Eschapasse [1], Grillo [2, 3], Pearson and colleagues [4], and Perelman and Koroleva [5]. Earlier reports are of interest largely for epidemiological and historical reasons [6, 7].

Meaningful long-term follow-up is scant. With the rarity of these tumors, a prolonged period of time is needed for any institution or group to accumulate sufficient numbers of cases. Furthermore, as we show, the types of tumors are sufficiently varied and the biological behavior of the tumors is sufficiently different that accretion of definitive data about the long-range results of treatment of any type is difficult. This is particularly true of one of the principal types of tracheal tumors, adenoid cystic carcinoma, which is notorious for its prolonged clinical course and insidious tendency to recur after many years.

This report details our experiences at Massachusetts General Hospital from November 1962 to July 1989, a period of more than 26 years, in treatment of primary tracheal tumors and the results achieved to date. The first case of this present series was indeed the first tracheal resection performed at Massachusetts General Hospital using contemporary techniques then under development. Thus, the series, to its detriment, reflects a period of learning about the application of surgical techniques, determination of possible extent of resection, and surgical management. The surgical techniques have been well described [8] and will be referred to only by category. The treatment of secondary tumors invading the trachea—from lung, thyroid, esophagus, and larynx—is not discussed.

Office records or hospital records, or both, of all patients were examined in detail. Current follow-up was pursued through telephone calls to patients, relatives and physicians, mail questionnaires, and in numerous cases, office visits and bronchoscopy.

Material and Methods

Patients

One hundred ninety-eight patients with primary tracheal tumors were evaluated in this period, including 2 patients whose lesions may be metastatic and who are described in detail. Not included were a number of patients referred for treatment of posttracheal resection stenosis without evidence of residual or recurrent tumor. Seventy of the 198 patients had primary squamous cell carcinoma of the trachea or carina (36% of the series), 80 had adenoid cystic carcinoma (40%), and the remaining 48 (24%) had a variety of lesions, benign and malignant. One hundred forty-seven patients underwent surgical resection of their tumors. Resection rates for the categories were: squamous cell carcinoma, 63%; adenoid cystic carcinoma, 75%; other tumors, 90%; and entire series, 74%. None of the squamous cell carcinomas were secondary to bronchogenic, laryngeal, or esophageal carcinoma. Adenoid cystic carcinoma confined to a main bronchus was not included. One hundred thirty-two patients (66% of the entire group) underwent resection with primary reconstruction of the airway (Table 1).

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Table 1. Primary Tracheal Tumors

Variable	Squamous	Adenoid Cystic	Other	Total
No. of lesions	70	80	48	198
Percentage of total	36	40	24	100
Surgical treatment	50	65	43	158
Excised	44	60	43	147
Percentage of type	63	75	90	74
Explored	6	5	0	11
Resection				
With reconstruction	41	50	41	132
Trachea	32	22	28	82
Carina	9	28	13	50
Laryngotracheal	1	4	2	7
Staged procedure	2	6	0	8

The group of tumors other than squamous cell and adenoid cystic carcinoma, although representing only about one quarter of the population, was composed of a multitude of tumor types and varying degrees of malignancy (Table 2), including both epithelial and mesenchymal neoplasms. Multiple squamous papillomas were not subjected to resection but were removed by cryotherapy, electrocoagulation, or laser treatment, depending on current technology. One of the patients with pleomorphic adenoma had had a similar tumor excised years before from a salivary gland. There had been no evidence of other metastases, and the lesion was therefore classified as a primary tracheal lesion. A patient with rhabdomyosarcoma had an isolated pedunculated lesion without extratracheal penetration; however, he had had a cervical rhabdomyosarcoma treated by a radical operation and intensive irradiation 6 years earlier but without evidence of local recurrence. No other foci developed. This may well have been a secondary lesion. The plexiform neurofibroma and the two paragangliomas were inextricably involved with the airway wall and appeared to have originated there. The vascular malformations involved arterial and venous components throughout the neck and mediastinum but had localized intraluminal obstructing protrusions. The small cell carcinoma was confined to the trachea, without any involvement or adherence of lung. The melanoma appeared to be solitary, without any previous known skin lesions and without evidence of retinal or other primary tumor. Additional patients with tumors of apparently mediastinal origin were excluded.

SEX. Squamous cell carcinoma occurred predominantly in men (52 men, 17 women). The distribution was similar to that of squamous carcinoma of the lung. Every patient with primary squamous carcinoma of the trachea was a cigarette smoker. In contrast, the male:female ratio of adenoid cystic carcinoma was essentially even (41:39). Smoking history in these patients appeared to be incidental. The distribution of the other tumors was fairly even, with 26 male and 22 female patients.

Table 2. Other Primary Tracheal Tumors

Type	No.
Benign	
Squamous papillomata	
Multiple	4
Solitary	1
Pleomorphic adenoma	2
Granular cell tumor	2
Fibrous histiocytoma	1
Leiomyoma	2
Chondroma	2
Chondroblastoma	1
Schwannoma	1
Paraganglioma	2
Hemangioendothelioma	1
Vascular malformation	2
Intermediate	
Carcinoid	10
Mucoepidermoid	4
Plexiform neurofibroma	1
Pseudosarcoma	1
Malignant fibrous histiocytoma	1
Malignant	
Adenocarcinoma	1
Adenosquamous carcinoma	1
Small cell carcinoma	1
Atypical carcinoid	1
Melanoma	1
Chondrosarcoma	1
Spindle cell sarcoma	2
Rhabdomyosarcoma	1

AGE INCIDENCE. Age incidence is shown in Table 3. Squamous cell carcinoma predominated in patients in their sixth and seventh decade. This is not dissimilar from the incidence of squamous cell carcinoma of the lung. Adenoid cystic carcinoma, on the other hand, was distributed between age 20 and 69 years, with a slight peak in the fifth decade. Other tumors showed a scattered distribution because of their variety of types; however, all

Table 3. Incidence of Primary Tracheal Tumors by Age

	No. of Tumors		
Age (yr)	Squamous	Adenoid Cystic	Other
1–10	...	...	4
11–19	...	...	8
20–29	1	13	11
30–39	1	16	9
40–49	9	19	5
50–59	29	15	6
60–69	24	13	4
70–79	6	5	1

tumors in children and young adults were in this category, and indeed, the number of these tumors decreased in the seventh decade.

Treatment

One hundred forty-seven of the 198 lesions were resected by the following modes: (1) resection and reconstruction of trachea or carina; (2) laryngotracheal resection, with or without cervicomediastinal exenteration; or (3) staged reconstruction with excision of the tumor in the hope of restoring airway continuity with cervical cutaneous tubes (Table 1). Eleven patients underwent exploration only, with or without institution of tracheostomy or T tube. Patients who simply underwent coring out of tumor, placement of T tube, or tracheostomy are not listed as surgically treated. This report focuses on the 132 patients who had resection and primary reconstruction. Seven underwent removal of larynx and trachea because tumor so involved the larynx that it could not be functionally salvaged. Eight patients underwent staged reconstructions. These procedures were performed when the extent of possible surgical resection was being explored. Because of their complications, high mortality, and the small number of patients who could be carried to completion, the procedure was abandoned. These patients, however, are included in this review as part of the total experience. Most unresected patients received radiotherapy.

Approximately equal numbers of patients with squamous cell carcinoma, adenoid cystic carcinoma, and other types of tumor were amenable to primary resection and reconstruction (41, 50, and 41 patients, respectively). However, the number of patients in each category subjected to tracheal resection, as distinct from carinal resection, varied markedly. Although approximately one third (37%) of patients who had primary reconstruction underwent carinal resection, in the case of adenoid cystic carcinoma, more than half were so treated. Only 9 of 41 patients with squamous carcinoma had carinal resection, reflecting the differing distribution of the tumors.

SURGICAL APPROACH. Operations were planned flexibly so that the approach would be adequate if unexpectedly longer lengths of trachea than anticipated were involved by tumor (Table 4). Upper tracheal tumors were explored through a cervical collar incision, with the option to extend exposure through the upper sternum. For midtracheal tumors, the option was kept open to extend the incision through full median sternotomy with the possibility of a transpericardial approach or through a "trapdoor incision" through the right fourth interspace. Lower tracheal tumors were most often approached through right thoracotomy. The earliest operations were performed electively through a trapdoor incision, which allows access to the entire trachea. Median sternotomy with transpericardial approach was used but offers less adequate exposure for extensive tumors.

Carinal resection was approached principally through a right posterolateral thoracotomy, in a few specific patients through a left thoracotomy, and in 3 patients through bilateral thoracotomy when carinal reconstruction with combined left pneumonectomy was anticipated. The modes of reconstruction are diagrammed in Figure 1.

Table 4. Surgical Approach to Resection and Reconstruction of Primary Tracheal Tumors

Approach	Squamous	Adenoid Cystic	Other	Total
Trachea				
Cervical	6	8	12	26
Cervicomediastinal	11	3	6	20
Transthoracic	12	10	10	32
Transpericardial	3	1	0	4
Carina				
Transthoracic	9	25	13	47
Bilateral transthoracic	...	3	...	3
Total	41	50	41	132

TECHNICAL FEATURES. In 9 patients (1 with squamous tumor; 3, adenoid cystic; 6, other) laryngoplasty (partial resection of the larynx) was necessary to establish adequate margins around a tumor. Each case was individualized. The trachea was tailored appropriately to mortise into the irregular defect thus created in the larynx. Due regard was paid to the recurrent laryngeal nerve and its functional state. This type of resection has been described in detail for management of secondary invasion of the airway by thyroid carcinoma [9].

Adjunctive procedures were used to lessen tension on the anastomosis, in addition to pretracheal dissection and cervical flexion. Laryngeal release was performed in 7 patients undergoing tracheal resection and in 5 undergoing carinal resection. We have since concluded on the basis of clinical observation, supported by experimental evidence, that laryngeal release does not generally translate to relaxation after carinal resection. It may be useful, however, in patients undergoing extensive resection of midtrachea along with the carina. Hilar release, which involved at least a U-shaped incision in the pericardium beneath the inferior pulmonary vein or complete circumcision of the pericardium around the hilum, was performed in 12 of 32 patients undergoing transthoracic tracheal resection and 23 of the 50 patients undergoing carinal resections. In addition, 4 patients with adenoid cystic carcinoma undergoing carinal resection had both laryngeal and hilar releases.

Ten patients had varying amounts of thyroidectomy performed to encompass tumors. Seven patients with tracheal tumors and 2 with carinal tumors underwent lateral removal of the esophageal wall, either muscularis alone or full thickness of the wall. The recurrent laryngeal nerve was deliberately sacrificed in four tracheal resections and in one carinal resection because of tumor involvement. Three patients with squamous carcinoma and 1 patient with sarcoma had omental pedicles brought up substernally for reinforcement of the suture line. All of these patients had previously received high-dose irradiation.

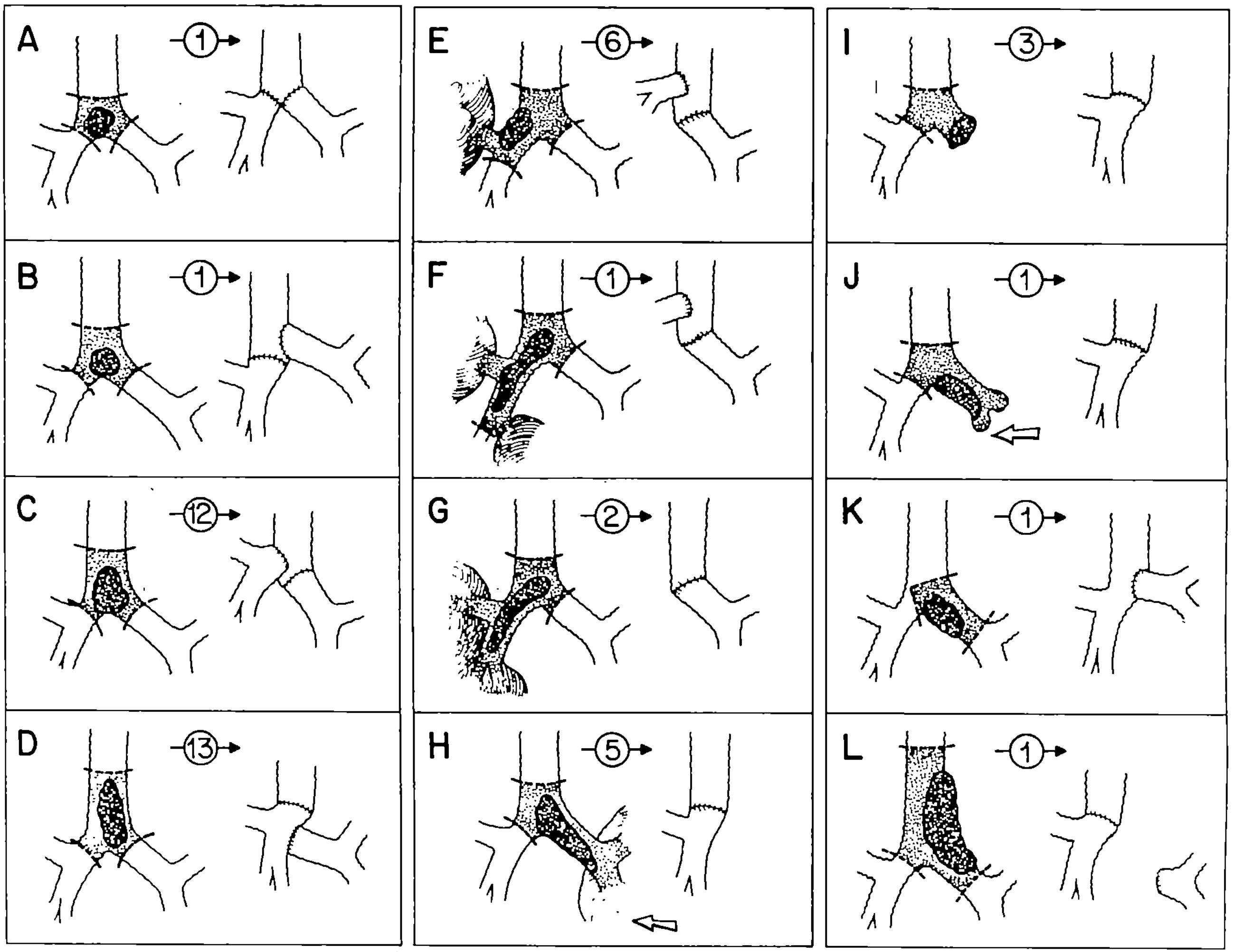

Fig 1. Modes of carinal resection and reconstruction used. Circled number *is number of patients.* Open arrows *indicate side of approach when not conventionally right sided. (A) Limited resection permits carinal restitution. (B) Technique used in initial carinal resection; technique in (A) would now be used. (C) More extensive resection. (D) Greater length of trachea. Technique of Barclay and co-workers [10]. (E) Involvement of right main bronchus and right upper lobe bronchus requires right upper lobectomy. (F) Middle lobe also removed. Right lower lobe bronchus may be anastomosed to left main bronchus. (G) Right carinal pneumonectomy. (H) Left carinal pneumonectomy. (I) Resection of carina after previous left pneumonectomy. (J) Resection of carina with extra long stump. (K) Wedge removal of left main bronchus from the right. (L) Tracheocarinal resection with long segment of left main bronchus. Exclusion of remaining left lung from the right. Left pneumonectomy also through bilateral thoracotomy.*

In 2 patients with tracheoesophageal fistula due to adenoid cystic carcinoma, in whom prolonged survival was possible, colon esophageal bypass with exclusion of the fistula was performed.

Results

Operative Results

COMPLICATIONS. In 2 patients undergoing tracheal resection anastomotic stenosis developed, in 1 after transient air leak. The second patient was operated on while still receiving high-dose steroids. Both patients later underwent re-resection successfully. Stenoses developed in 4 patients after carinal resection. Two patients who had undergone pneumonectomy with carinal resection underwent re-resection successfully, 1 through a cervical incision because the anastomosis was so high. Two others required upper lobectomy of the reimplanted right lung with reattachment of the bronchus intermedius or lower lobe. Both procedures were successful. Three air leaks were handled conservatively with success. Four patients developed suture line granulomas in the era before absorbable sutures were used. These were managed bronchoscopically. One patient in whom laryngoplasty had been performed showed an elevation of the posterior mucosal flap, which healed in place after brief intubation. One esophageal fistula occurred after transthoracic tracheal resection with extensive full-thickness resection of the esophageal wall. A small fistula healed spontaneously. Vocal cord paralysis, reversible with time in some cases, occurred in 8 patients undergoing tracheal or carinal resection for squamous carcinoma and in 3 patients undergoing tracheal or carinal resection for adenoid cystic carcinoma. Six patients experienced aspiration on deglutition, principally after laryngeal release necessitated by extended resection. Most resolved with time, although rarely temporary gastrostomy was required. One patient had a small empyema treated after transthoracic tracheal resection by drainage. In 1 patient, Guillain-Barré syndrome developed.

In 2 patients, pulmonary edema developed acutely after carinal resection with right pneumonectomy. Three others had pneumonia. One patient who underwent carinal resection with anastomosis of the right main bronchus and exclusion of the left lung had hypoxemia. The pulmonary artery had not been ligated. Later, left pneumonectomy was required to remove the nonfunctioning but shunting lung [11].

OPERATIVE DEATHS. There were 7 operative deaths in the 132 patients undergoing primary resection and reconstruction (5%) (Table 5). One death occurred in the 82 tracheal reconstructions (1%), but six occurred among the 50 carinal reconstructions (12%). The highest mortality (4) occurred in carinal resections of adenoid cystic carcinoma, probably due to excessive tension after extended resection for this infiltrating disease. One death after tracheal resection and reconstruction resulted from anastomotic leakage followed by pneumonia. Of patients who underwent carinal resection and reconstruction, respiratory failure developed in 2 after leakage of the anastomosis; 1 patient had respiratory failure after development of postoperative pulmonary edema, and 1 had a sudden massive hemorrhage on the ninth postoperative day, presumably from the pulmonary artery.

No death occurred in the 7 patients with laryngotracheal tumors (with or without cervicomediastinal exenteration). Mortality was unacceptably high in the patients undergoing staged reconstruction (5 of 8 patients), and the procedure has been abandoned. Three of 9 patients who underwent exploration alone died. Deaths after exploration were in 1 patient the result of hemorrhage from the innominate artery after establishment of a mediastinal tracheostomy in continuity and in 2 others the result of respiratory failure. The deaths after staged reconstruction were the result of anastomotic separation in 2 patients, respiratory failure in 1, hemorrhage from the innominate artery in 1, and hypoxemia related to use of cardiopulmonary bypass with extensive manipulation of the right middle and lower lobe to accomplish reconstruction in a patient with only a left upper lobe on the opposite side.

Table 5. Results of Surgical Treatment of Primary Tracheal Tumors

Variable	Squamous	Adenoid Cystic	Other	Total
No. of tumors resected	44	60	43	147
Operative deaths (resection)	3	8	1	12
Resection, reconstruction				
Trachea	1	0	0	1
Carina	1	4	1	6
Percent (resection, reconstruction)	5	8	2	5
Laryngotracheal	0	0	0	0
Staged procedures	1/2	4/6	0	5
Exploration only	2/6	1/3	0	3
Survival (resected tumors)				
Dead				
Of tumor	13	7	3	23
Of other cause	6	5	1	12
Alive				
With tumor	0	1	0	1
Without tumor	20	39	35	94
Lost to follow-up	2	0	3	5

Two additional deaths were the result of technical failure of the operation, although they occurred many months later in other jurisdictions. One patient had undergone a carinal resection with reconstruction, and the other had a staged resection. Stenosis developed in both, and 1 was probably also having continued aspiration from laryngeal malfunction. Further treatment would have been advisable in both cases.

Oncologic Results

Of the 147 patients who underwent resection for tumor (including patients with primary reconstruction and those without), 135 survived operation. Seventy percent of these are currently alive without tumor. Forty-nine percent of patients with squamous cancer, 75% of patients with adenoid cystic tumors, and 83% of the other patients are alive and disease-free. Table 5 shows the number of patients in each category who have died of tumor or of other causes and the number who are alive with known carcinoma. Interpretation of these figures is difficult because the cases are spread over many years. Because more patients have been referred for treatment in the last 10 years, and especially in the last 5 years, this reflects favorably in the number of patients living without known disease. Nonetheless, the figures appear to be encouraging.

If we consider patients who had squamous cell carcinoma and are living without known disease, 10 patients were operated on more than 3 years ago; another 4 died of other disease or had been followed for 5, 7, 8, and 15 years disease-free (Table 6). This represents 14 patients probably cured of their cancer. An additional 10 are free of disease but were treated within the last 3 years. This is a clinically significant interval for squamous cancer of the trachea, which tends to recur early, in approximately the same time frame as squamous carcinoma of the lung. One patient had two primary carcinomas of the trachea widely separated in time and location. The first was resected in 1981 and the second in 1985. Recurrence of the second carcinoma occurred in 1989. Additional significance is given these results because all patients who died of recurrent squamous cell carcinoma of the trachea did so within 4 years of resection.

The first patient who underwent a resection (of the carina) for adenoid cystic carcinoma in this series was disease-free until recurrence at the suture line 17 years

Table 6. Survival After Resection of Tracheal Carcinoma

Variable	Squamous	Adenoid Cystic
Operative deaths	3	8
Alive without carcinoma		
>10 yr	3 (9)[a]	5 (11)
5–10 yr	4 (10)	11 (12)
3–5 yr	3 (6)	10 (11)
0–3 yr	10 (11)	13 (13)
Died of carcinoma		
>10 yr	0	4
5–10 yr	0	1
3–5 yr	5	2
0–3 yr	8	0
Died without carcinoma; lost		
>10 yr	1	0
5–10 yr	3	0
3–5 yr	1	1
0–3 yr	3	4
Alive with carcinoma	0	1

[a] Original number of operative survivors, excluding those who died of other causes later, is shown in parentheses.

later. Because her resection margins and lymph nodes had been negative, no irradiation had been given. Bronchoscopic follow-up had been terminated after 10 years. Because this type of tracheal carcinoma has such proclivity for a long clinical course and late recurrence, it is more difficult to interpret results of its resection. Sixteen patients are living without evidence of recurrent disease who were operated on more than 5 years ago. Twenty-three additional patients who have undergone resection are living without known disease. The long-term outlook with adenoid cystic carcinoma is less clear (Table 6). Five patients operated on more than 10 years ago are living without disease, but 4 died of late metastases or recurrence after 10 years. On the other hand, 3 have died of recurrence or metastasis in 3 to 10 years, whereas 21 are alive for between 3 and 10 years without evidence of recurrent disease. These figures emphasize the sharp decrease in number of patients free of squamous carcinoma after 3 years with little further decrease. Patients with adenoid cystic carcinoma, on the other hand, remain disease-free for many years but appear to be threatened by late recurrence.

As might be expected in the heterogeneous group of other tumors, statistical results are good, because many of these tumors were benign or of low-grade malignancy. One of the 11 carcinoids was highly atypical and had metastasized to regional lymph nodes in highly malignant fashion. All mucoepidermoid tumors behaved benignly. Adenocarcinoma occurred in a child in the membranous wall of the carina in the base of a cyst. This has not recurred in more than 3½ years. The single patient with adenosquamous carcinoma had a tumor that involved the larynx to such an extent that it could not be saved. The patient died of metastasis 4⅔ years later. A single patient with small-cell carcinoma confined to the trachea had subsequent chemotherapy and radiation because of the histological appearance of the tumor. He is without recurrence 3⅔ years after resection. The single patient with melanoma has no history of previous cutaneous lesions and no current cutaneous or retinal lesions, but follow-up is brief. No other metastatic disease has been detected, and it is believed that this is indeed a primary lesion of the airway. The patient who had pseudosarcoma remains disease-free 19 years later. Several patients reported with this disease in the era before extended tracheal resection died of strangulation due to local growth without metastasis. The chondrosarcoma was of low grade, but the patient died of pulmonary metastases slightly more than 5 years after resection. The patient with rhabdomyosarcoma died of osteogenic sarcoma probably due to irradiation treatment received for his previous cervical rhabdomyosarcoma in early childhood. The remaining death from tumor was that of a patient who had a spindle cell sarcoma of the carina.

Five patients with other tumors had operations for the same tumor before referral. Three had carcinoids removed incompletely, with recurrences from 10 to 14 years later. An 8-year-old child with malignant fibrous histiocytoma had a previous incomplete resection by a local plastic procedure at the carina. She remained disease-free for 3 years after carinal resection but has been lost to follow-up. A 19-year-old patient with a fibrous tumor of the carina underwent prior pneumonectomy with residual tumor left at the carina. He remains disease-free nearly 2 years after carinal resection. Two patients were lost to follow-up: 1 had a low-grade spindle cell sarcoma and was followed for 10 years, and the other had a solitary squamous papilloma and was followed for 7 years, both without recurrence. One patient with granular cell tumor high in the trachea involving the lower posterior larynx was later found to have a concurrent granular cell tumor of the bronchus intermedius, which was removed by sleeve resection.

EFFECT OF TUMOR AT RESECTION MARGINS AND IN LYMPH NODES. The finding of tumor at the resection margins, even by frozen section during operation, has particular importance in airway reconstruction. Because of the requisites for reconstruction, it is sometimes impossible to resect more airway without endangering the safety of the anastomosis by creating excessive anastomotic tension. Furthermore, extensive regional lymph node dissection may destroy the blood supply to the trachea. Loss of blood supply can lead to necrosis at the anastomosis, followed by irreparable stenosis. Therefore, only immediately adjacent regional lymph nodes are blocked out with the specimen. Others may be sampled for prognostic information. Table 7 shows the distribution of involved lymph nodes and margins for both squamous cell carcinoma and adenoid cystic carcinoma in two critical groups of patients: those who died with cancer and those who are alive without known cancer. The clinical significance of the findings appears to differ in the two types of carcinoma.

Positive lymph nodes in squamous cell carcinoma were

Table 7. Effect on Survival of Tumor at Margins and in Lymph Nodes at Resection

Variable	Died With Cancer	Alive, No Cancer
Squamous cell (No.)	13	22
Nodes positive	6	2
Margins positive		
Invasive	4	1
In situ	0	6
Nodes, margins negative	3	12
Adenoid cystic (No.)	7	38
Nodes, margins positive	3	16
Nodes, margins negative	4	22

Almost all patients received postoperative radiotherapy.

more commonly found in patients who later died with cancer than in those who survived without cancer. The 6 patients with positive nodes are from a total of 13 who died of cancer. Only 2 patients of the 20 disease-free patients had positive nodes. Invasive carcinoma at the resection margin is of graver consequence than in situ carcinoma; 4 of 5 patients with invasive carcinoma died. In contrast, all 6 patients with in situ disease are disease-free. Essentially all these patients have undergone radiotherapy in doses varying from 4,500 to 6,500 rads. Because irradiation was administered in many centers around the world, it was impossible to control dosage or portals. With adenoid cystic carcinoma accompanied by positive margins, lymph nodes, or both, little effect appears evident in comparison with patients with negative margins and nodes. Because of the proclivity of this tumor to extend for long distances submucosally and perineurally, the finding of malignant cells at a distance from the gross tumor is all too common. The surgeon must often compromise total resection for safety. All these patients now receive postoperative irradiation. Suture line recurrence thus far has been rare. Late recurrence has been in lung, bone, liver, or brain. In contrast, irradiation of unresected tumor is all but uniformly characterized by local recurrence in 3 to 5 years despite early good response.

OTHER SQUAMOUS CELL CARCINOMA. Sixteen (40%) of 40 patients who had resection of squamous carcinoma of the trachea had either a previous history, a concurrent finding, or later occurrence of squamous cell carcinoma in the respiratory tract. One had concurrent squamous cell carcinoma of the tongue. One patient had carcinoma of the larynx treated before tracheal resection and a second later had carcinoma of the larynx. In 1 patient, previously noted, a second primary carcinoma of the trachea developed at a different level. Seven patients had received prior treatment for squamous carcinoma of the lung by lobectomy or pneumonectomy, and in 5, squamous cell carcinoma of the lung developed later. Of these 12 patients, 2 of whom had two primary squamous carcinomas of opposite lungs at wide time intervals, 3 died of recurrent tracheal carcinoma, 1 died of recurrence of prior carcinoma of the lung, 1 died of a later carcinoma of the lung, and 1 will soon die of a second primary carcinoma of the lung with a tracheal resection between the two pulmonary episodes. Four patients who underwent lung resection either preceding or subsequent to the tracheal resection were living without disease from 2½ to 15 years after the tracheal episode.

ROLE OF IRRADIATION. In view of the narrow margins often obtainable in tracheal resection, even when the margins and lymph nodes are histologically negative, we have deemed it prudent to use postoperative irradiation for both squamous cell and adenoid cystic carcinoma of the trachea. Both are sensitive to irradiation, particularly adenoid cystic carcinoma. After recurrence of adenoid cystic carcinoma in a nonirradiated patient 17 years after resection, it appeared all the wiser to use irradiation subsequent to operation. Irradiation alone has been argued to be appropriate primary treatment for carcinoma of the trachea [12]. In an effort to clarify this question, we have compared patients who underwent resection (with or without subsequent radiotherapy) with those who received radiotherapy alone as primary treatment. A few also underwent exploration. Admittedly, the principal reason for assigning patients to the radiotherapy category was extent of tumor. This, however, was frequently longitudinal extension and did not necessarily indicate a large bulk of neoplasm. For each type of tracheal carcinoma and for each treatment method (operation and irradiation versus irradiation alone), we have noted the number of patients dead of disease and those alive without disease for more than 1 year (Table 8). The spectrum of patients is scattered over a broad time scale, so that comparison is not precise.

With squamous cell carcinoma of the trachea, of patients who underwent what we consider optimal therapy—surgical resection followed by radiotherapy—11 patients have nonetheless died of carcinoma of the trachea. Eighteen remain alive for periods of more than 1 year without evidence of disease. In marked contrast, 16 patients for whom radiotherapy was essentially the only treatment method are dead of carcinoma. One remains alive approximately 7 years after treatment.

Patients with adenoid cystic carcinoma have been divided into those who have died of their carcinoma and

Table 8. Treatment of Tracheal Tumor: Resection Versus Irradiation

Tumor Type	Dead of Carcinoma	Alive (>1 yr) Without Carcinoma
Squamous		
Resection (± irradiation)	11	18
Irradiation (± exploration)	16	1
Adenoid cystic		
Resection (± irradiation)	7	38
Irradiation (± exploration)	9	3

those who are alive without known disease. Analysis is more difficult in these patients because the disease may have long periods of apparent control after either operation or irradiation. Of patients treated with operation (and usually postoperative radiotherapy) 7 are dead of carcinoma and 38 are alive without known disease. With irradiation alone, 9 are dead of carcinoma and only 3 are alive without evidence of disease.

In an effort to determine whether there is palliative benefit to patients who undergo operation, given its risks, in combination with radiotherapy in comparison with radiotherapy alone, survival of patients with squamous carcinoma receiving one or the other treatment method but who nonetheless died of carcinoma has been examined. Table 9 shows the number of surviving patients in 12-month periods. The results of radiotherapy alone are much like those obtained for squamous carcinoma of the lung, with most patients showing recurrence in 2 years. In contrast, resection with radiotherapy provides 2 to 4 years of survival. Because the course of adenoid cystic carcinoma is such a prolonged one, we have examined similar treatment groups with the same endpoint of death from disease, both for squamous and adenoid cystic carcinoma, by comparing median and average survival in months (Table 10). Resection combined with irradiation, given the limits of this nonrandomized comparison, provides a tripled survival time for squamous cell carcinoma and at least a tripled survival time for adenoid cystic carcinoma.

Comment

The analysis of this 26-year experience with surgical management of primary tumors of the trachea appears to confirm and extend conclusions based on previously reported experiences. Eschapasse [1] collected 152 primary tracheal tumors from multiple teams in France and the USSR and reported in 1974 on 121 patients surgically treated, 75 reconstructed after cylindrical resection and anastomosis (47) or carinal resection (28). There were 13 deaths in 121 operations. Five of 19 patients with adenoid cystic tumors were alive and free of disease for 3 to 9 years, and 11 of 27 patients with squamous carcinoma were alive and free of disease for 7 months to 16 years. In 1987, Perelman and Koroleva [5] reported a 20-year experience (1963 to 1983) with 116 open operations in 135 patients; 75 were treated by sleeve resection (41) or carinal resection (34), with 11 deaths. Overall survival for squamous cell carcinoma was 27% at 3 years and 13% at 5 and 10 years; for adenoid cystic carcinoma, overall survival was 71% at 3 years, 66% at 5 years, and 56% at 10 and 15 years. Pearson and colleagues [4] also reported surgical treatment of 44 patients between 1963 and 1983. Twenty-nine underwent reconstruction, including 16 sleeve resections and 13 carinal resections, with 2 deaths. Nine patients with adenoid cystic carcinoma were alive without disease at 1 to 20 years after operation, 3 had died of other disease in 6 to 18 years, and 2 were alive with disease. Four of 6 patients with squamous carcinoma who underwent resection were alive at 6 to 56 months.

Table 9. Palliative Value of Operation and Irradiation for Squamous Cell Tracheal Carcinoma

Time to Death From Carcinoma (mo)	Irradiation Only	Resection (± Irradiation)
<12	5	1
12–24	3	2
24–36	1	4
36–48	0	4
>48	1	0

Table 10. Duration of Survival: Irradiation Versus Operation (± Irradiation)

	Survival (mo)	
Variable	Median	Average
Squamous carcinoma		
Irradiation only	10	11
Resection (± irradiation)	34	31
Adenoid cystic carcinoma		
Irradiation only	28	39
Resection (± irradiation)	118	107

The following therapeutic recommendations appear to be justified by the experience noted and the data presented: First, benign primary tumors of the trachea and tumors of intermediate aggressiveness are best treated by surgical resection with reconstruction of the airway. Second, primary squamous cell carcinoma and adenoid cystic carcinoma of the trachea are best treated by resection when primary reconstruction may be safely accomplished. Resection should probably be followed by full-dose mediastinal irradiation in most cases. Third, malignant primary tracheal tumors of other types should also be resected if such resection will permit safe primary reconstruction. Irradiation should probably be administered postoperatively in most such patients.

The surgical mortality and morbidity described in this report will undoubtedly be improved in the years ahead on the basis of experience obtained over the last quarter century. It appears judicious that extensive tracheal reconstruction, in particular that of the carina, be accomplished in centers where major efforts are made in this type of surgery.

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DISCUSSION

DR PETER C. PAIROLERO (Rochester, MN): I would like to thank Drs Grillo and Mathisen for reporting what is surely the largest series of tracheal resections for neoplasms in the world. One hundred forty-seven patients undergoing resection with only 12 operative deaths is truly amazing, when one considers that the time period transgressed 26 years, and that five of these deaths occurred in their early experiences after eight staged tracheal reconstructions, a procedure that Dr Grillo subsequently abandoned.

Clearly Grillo and Mathisen have amply demonstrated that tracheal resection, if at all possible, is the treatment of choice for these neoplasms. A 10-year survival of approximately 45% for cylindroma and 33% for squamous cell carcinoma attests to the value of resection. They have also demonstrated that squamous cell carcinoma tends to recur early after resection and cylindroma late, and that both cancers are stage dependent, with lymph node metastases having an ominous effect on survival.

Because of the inherent difficulty in extended tracheal resections, Grillo and Mathisen have recommended postoperative radiation therapy in an attempt to control late recurrence. However, it is difficult to know what effect irradiation had on survival because the exact course of cancer deaths was never specified. I would presume, however, that many of the patients died of distant metastases, which are unpreventable by irradiation, rather than local recurrence. Nonetheless it is entirely possible, but unproven, that irradiation did reduce the incidence of local recurrence.

The role of preoperative irradiation is unaddressed in this report. Perhaps, Dr Grillo, you could give us your thoughts on this. Will preoperative radiation therapy reduce tumor size and allow a longer margin of tumor-free trachea to be resected?

There were 12 operative deaths in this series; 5 or 42% were from tracheal dehiscence secondary to excessive anastomotic tension. Certainly excessive tension will always be a problem, because the tendency to resect more trachea is always present. Dehiscence will also increase if healing is impaired by other factors such as infection, steroids, or irradiation. To prevent this complication, Dr Grillo did use the omentum to reinforce the anastomosis in 4 patients. Should omentum or perhaps muscle be used to reinforce more tracheal anastomoses? Certainly either could be done with little additional morbidity. What then, Dr Grillo, are your indications for tracheal reinforcement? Finally, are we in 1989 any closer to a tracheal substitute?

DR GRILLO: Thank you, Dr Pairolero, for your comments. I will try to answer your questions as quickly as possible, but it's quite a battery.

Most of the deaths from carcinoma were from distant metastases. Local recurrence was not that much of a problem. We admit that we do not have any randomization. As you can see, with these small numbers we had to decide on a way to treat these tumors and go at it.

I was perhaps unduly influenced by the course of the first patient in whom I ever performed resection. It was a carinal resection for adenoid cystic carcinoma; the nodes and margins were negative. After 10 years I stopped following her, and in the 17th year she returned with recurrence at the suture line, which proved fatal. An experience or two like that impels you to do what you can to prevent suture line recurrences.

I'm afraid we can't answer the question of what precisely contributes to long-term survival, except to say that many patients with tumor microscopically present at the resection margins (known at the time of resection but in cases where we could not resect any more trachea) had postoperative irradiation and are alive without recurrence. So we feel there is a value to it, if only on this basis.

The group in Toronto has used preoperative irradiation, again in adenoid cystic carcinoma. We cannot really deduce much from this, I believe, because again there is no comparative series. We have not tried to reduce bulk by irradiation before resection in this group of patients.

On the question of reinforcement, we have used the omentum only in those 4 patients who had heavy irradiation, often at remote times—over 1 year—which meant that the healing ability of the tissues would be diminished. All were successful and did heal well. This followed a very bad experience in thyroid cancer many years before without augmentation after high-dose irradiation.

In a few patients we have used intercostal muscle for buttressing after a previous operation elsewhere had failed. I do not think it will actually prevent separation. It might prevent leak, but you would end up with stenosis if the tissue separated underneath the flap. Incidentally, if you use an intercostal muscle wrapped circumferentially, remove the periosteum or you will get an obstructing grommet of bone.

The last question was about prosthetics. I don't know what the solution to that will be. I can only reiterate the basic problem with tracheal prostheses: placing a foreign body in an epithelial-lined tube sets up a chronic ulcer bed in relation to the prosthesis. This chronic reaction leads to granulation, obstruction, and hemorrhage, often as a late incident. No material has yet been developed that becomes incorporated in the tissue structure. Composite graft replacements that we and others have worked at in the laboratory are too complex and have too many complications to be used safely in people.

Cerebrospinal Fluid Drainage and Steroids Provide Better Spinal Cord Protection During Aortic Cross-Clamping Than Does Either Treatment Alone

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We investigated whether intravenous methylprednisolone (30 mg/kg) before 30 minutes of aortic cross-clamping and after 4 hours could enhance the effects of cerebrospinal fluid drainage on spinal cord perfusion pressure and postoperative paraplegia when proximal blood pressure was controlled with sodium nitroprusside and partial exsanguination. Dogs were randomized into three groups: group 1 (n = 6), control; group 2 (n = 7), steroids; and group 3 (n = 6), steroids with cerebrospinal fluid drainage. During aortic cross-clamping, blood pressure proximal to the clamp decreased significantly in each group compared with baseline ($p < 0.05$), but did not differ among groups (group 1 = 82.2, group 2 = 82.1, group 3 = 86.6 mm Hg, $p > 0.05$). Mean distal pressure decreased from systemic values to 8.4, 8.5, and 3.7 mm Hg, respectively, after aortic cross-clamping ($p < 0.05$); these values did not differ from one another ($p > 0.05$). During aortic cross-clamping, cerebrospinal fluid pressure in groups 1 and 2 did not differ significantly compared with baseline (12.2 versus 8.2, 14.2 versus 10.7 mm Hg, $p > 0.05$), whereas in group 3 the baseline cerebral spinal fluid pressure of 10.7 mm Hg decreased to 0.4 mm Hg ($p < 0.05$). Spinal cord perfusion pressure in group 3 was significantly higher than in groups 1 and 2 (3.3 versus −3.9 and −5.7 mm Hg, $p < 0.05$), but did not differ between groups 1 and 2 ($p > 0.05$). Somatosensory evoked potential loss occurred significantly earlier in groups 1 and 2 than in group 3 (4 minutes 31 seconds and 4 minutes 18 seconds vs 11 minutes 16 seconds, $p < 0.05$). No significant difference in the time to somatosensory evoked potential loss was noted between groups 1 and 2 ($p > 0.05$). Paraplegia rates differed significantly between groups 3 and 1 (1/6 versus 5/6 paralyzed, $p < 0.05$), but were not different when group 3 was compared with group 2 (1/6 versus 3/7 paralyzed, $p > 0.05$). This study shows that steroids with cerebrospinal fluid drainage provide spinal cord protection during aortic cross-clamping, whereas steroids alone are ineffective.

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Cross-clamping of the thoracic aorta during resection of thoracic or thoracoabdominal aneurysms causes proximal hypertension that must be controlled either pharmacologically or with use of shunts or bypasses. Sodium nitroprusside (SNP) remains the most widely used agent for control of blood pressure during aortic operations [1, 2]. It has been experimentally shown to have detrimental effects on spinal cord perfusion, however, because it reduces distal aortic blood pressure (D-BP) and causes an increase in cerebrospinal fluid pressure (CSFP) [3].

Cerebrospinal fluid drainage (CSFD) improves spinal cord perfusion pressure (SCPP) and decreases paraplegia rates after aortic operations [4, 5], but it is ineffective in an experimental model when SNP is used to control proximal hypertension [6].

Steroids can lengthen the warm ischemic time of the spinal cord [7] by acting as free radical scavengers [8], stabilizing membranes [9], and reducing spinal cord edema [10], but they have not been used either experimentally or clinically in association with CSFD. Because the postulated mechanism of CSFP increase during SNP infusion is a loss of compliance of the spinal canal secondary to edema of the spinal cord [3], and the ineffectiveness of CSFD may be related to the edema of the spinal cord, we designed a study to evaluate whether steroids could enhance the effects of CSFD on cerebrospinal fluid dynamics and neurological outcome in a canine model in which SNP and partial exsanguination were used to control proximal hypertension.

Material and Methods

Nineteen mongrel dogs weighing 25 to 35 kg were anesthetized with intravenous pentobarbital sodium (20 mg/kg) and fentanyl (4 μg/mL). Animals were intubated and placed on a Harvard ventilator using room air. Respirator settings included a tidal volume of 12 mL/kg, respiratory rate to maintain the partial pressure of carbon dioxide between 25 and 35 mm Hg, and 5 cm H_2O of positive end-expiratory pressure.

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Pressure-monitoring catheters were inserted into the left carotid and femoral arteries and left jugular vein to monitor aortic pressures proximal and distal to the cross-clamp and central venous pressure. A 20-gauge, 1.5-inch (37.5 mm) spinal needle was inserted percutaneously into the cisterna cerebellomedullaris to monitor CSFP. All pressures were monitored with Bentley Trantec physiological pressure transducers (model 60-800; Santa Ana, CA). Intravenous fluids (lactated Ringer's solution) were administered to maintain a central venous pressure of 3 to 5 mm Hg.

Somatosensory evoked potentials (SEPs) were monitored using previously described techniques [11]; SEP waveforms were recorded every minute during the cross-clamp interval. The time required to identify a morphologically flat waveform (on two consecutive measurements) was designated as SEP loss.

Through a left thoracotomy in the fourth intercostal space, the aorta was isolated 1 cm distal to the left subclavian artery. Baseline SEPs, proximal aortic blood pressure (P-BP) and D-BP, and CSFP were measured after a ten-minute stabilization period.

Proximal blood pressure was controlled to a mean of 85 mm Hg by removing 40% of the estimated circulating blood volume through the left carotid arterial catheter before application of the aortic cross-clamp. In addition, SNP (50 mg in 250 mL of 5% dextrose in water) was infused at a rate of 15 to 45 μg/kg/min throughout the experimental interval.

Methylprednisolone sodium succinate (30 mg/kg) was administered intravenously ten minutes before cross-clamping and repeated after four hours in groups 2 (n = 7) and 3 (n = 6). In addition, in group 3 cerebrospinal fluid was drained, using previously described techniques [12]. Group 1 (n = 6) controls received no treatment.

The aorta was cross-clamped at the previously isolated site for 30 minutes. All variables were monitored every minute until termination of the experiment. One minute before release of the aortic cross-clamp, 44.6 mEq of sodium bicarbonate was administered intravenously, and the shed blood was slowly retransfused.

The animals were allowed to recover, and at 48 hours postoperatively their neurological status was evaluated by an observer unaware of the experimental protocol using Tarlov's criteria [13]: grade 0, spastic paraplegia and no movement of the lower limbs; grade 1, spastic paraplegia and slight movement of the lower limb joint; grade 2, good movement of the lower limbs, but unable to stand; grade 3, able to stand but not able to walk normally; grade 4, complete recovery. Animals were then killed in compliance with the guidelines of the 1986 report of the American Veterinary Medical Association Panel on Euthanasia [14].

All animals received humane care and treatment in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85–23, revised 1985).

All data are reported as the mean ± the standard deviation, and were analyzed using analysis of variance, Student-Newman-Keuls test, and Fisher's exact test. Statistical significance was accepted at a p value of less than 0.05.

Table 1. Hemodynamics[a]

Group	Baseline P-BP	Baseline D-BP	Aortic Cross-Clamping P-BP	Aortic Cross-Clamping D-BP
1	104 ± 15.2	105 ± 15.2	82.2 ± 5.4[b]	8.4 ± 6.0[b]
2	104.6 ± 15.7	105.7 ± 15.8	82.1 ± 5.0[b]	8.5 ± 4.1[b]
3	107.2 ± 11.8	107.3 ± 14.6	86.6 ± 5.0[b]	3.7 ± 1.8[b]

[a] Data are shown as mean values plus or minus standard deviation in millimeters of mercury. [b] Significance: $p < 0.05$ versus baseline.

D-BP = distal blood pressure; P-BP = proximal blood pressure.

Results

Hemodynamics and Cerebrospinal Fluid Dynamics

There was no significant difference in mean P-BP, D-BP and CSFP among the three groups at baseline. After aortic cross-clamping, while SNP was being infused, P-BP decreased significantly from systemic baseline values to 82.2 ± 5.4 mm Hg in group 1, 82.1 ± 5 mm Hg in group 2, and 86.6 ± 5 mm Hg in group 3 ($p < 0.05$ versus baseline). These values were not significantly different from each other ($p > 0.05$). Mean D-BP decreased from systemic values to 8.4 ± 6 mm Hg, 8.5 ± 4.1 mm Hg, and 3.7 ± 1.8 mm Hg, respectively, in the three groups ($p < 0.05$ versus baseline, $p > 0.05$ versus each other) (Table 1).

Cerebrospinal fluid pressure did not change significantly from its baseline value while the aorta was cross-clamped in groups 1 and 2; CSFP was significantly reduced to 0.4 ± 0.4 mm Hg by CSFD in group 3 ($p < 0.05$ versus groups 1 and 2) (Table 2). This difference remained statistically significant throughout the aortic cross-clamp interval ($p < 0.05$). The CSFPs at each five-minute interval were not significantly different within or between groups 1 and 2 (Fig 1). No significant change at similar intervals was noted in group 3 after the initial statistically significant decrease ($p < 0.05$) caused by CSFD.

Spinal cord perfusion pressure (defined as D-BP minus CSFP) was −3.9 ± 5.8 and −5.7 ± 5.5 mm Hg during the aortic cross-clamp interval in groups 1 and 2, respectively, whereas it remained significantly higher at 3.3 ± 1.9 mm

Table 2. Cerebrospinal Fluid Dynamics[a]

Group	Baseline CSFP	Baseline SCPP	Aortic Cross-Clamping CSFP	Aortic Cross-Clamping SCPP
1	8.2 ± 3.1	96.8 ± 9.1	12.2 ± 3.6	−3.9 ± 4.8
2	10.7 ± 2.6	95.0 ± 9.2	14.2 ± 4.6	−5.7 ± 4.8
3	10.7 ± 4.5	96.6 ± 8.1	0.4 ± 0.4[b]	3.3 ± 1.1[c]

[a] Data are shown as mean values ± standard deviation in millimeters of mercury. [b] Significance: $p < 0.05$ versus baseline. [c] Significance: $p < 0.05$ versus groups 1 and 2.

CSFP = cerebrospinal fluid pressure; SCPP = spinal cord perfusion pressure.

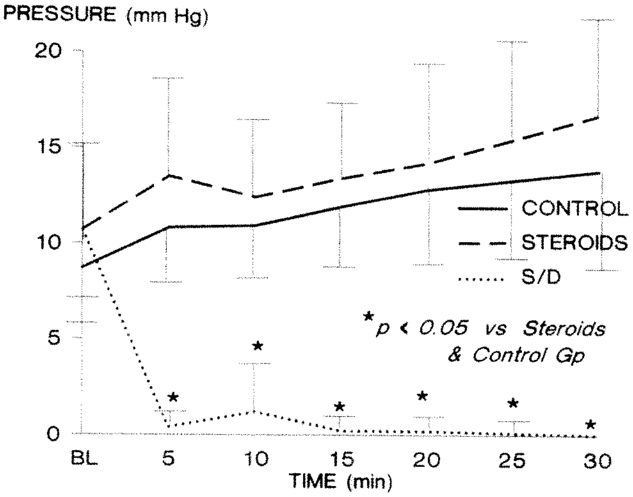

Fig 1. Comparison of cerebrospinal fluid pressures of control group, steroid group, and group with steroids plus cerebrospinal fluid drainage (S/D) at baseline (BL) and during the aortic cross-clamp interval.

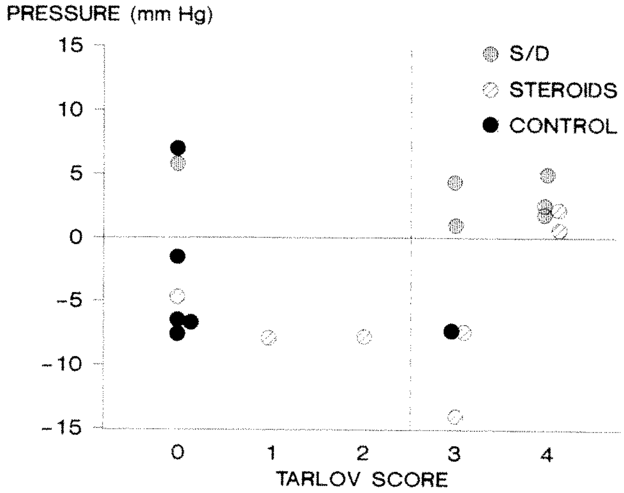

Fig 3. Spinal cord perfusion pressures versus neurological outcome (Tarlov score [13]) of control group, steroid group, and group with steroids plus cerebrospinal fluid drainage (S/D).

Hg in group 3 ($p < 0.05$ versus groups 1 and 2); SCPP did not differ between groups 1 and 2 ($p > 0.05$) (Fig 2).

The three groups received similar total amounts of SNP: 27 ± 12, 24 ± 9, and 31 ± 8 mg, respectively, to control P-BP ($p > 0.05$). The total amount of blood removed was also similar among the three groups: 933 ± 216, 993 ± 124, and 975 ± 173 mL, respectively ($p > 0.05$).

Neurological Injury

For statistical analysis, animals were subdivided into animals with minimal or no injury (Tarlov grades 3 and 4) and those unable to ambulate (Tarlov grades 0–2). There was a significant difference in the neurological injury sustained in the three groups (Fig 3). All but 1 animal in group 3, with positive SCPP, were graded as Tarlov 3 or 4, whereas 5 of 6 animals in group 1 suffered spastic paraplegia. Animals in group 2 had a somewhat varied neurological outcome, with only 3 of 7 animals suffering severe neurological injury. Statistical analysis showed a significantly better neurological outcome of group 3 animals as compared with controls ($p < 0.05$). No difference was noted when group 2 was compared with either group 1 or 3 ($p > 0.05$). In addition, a comparison between animals with positive SCPP and those with negative SCPP showed that 2 of 9 animals with positive SCPP were neurologically injured, whereas 7 of 10 animals with negative SCPPs suffered paraplegia ($p < 0.05$).

Somatosensory Evoked Potential Changes

Time until SEP loss (Fig 4) was significantly longer at 11 minutes 16 seconds in group 3 (positive SCPPs) as compared with groups 1 and 2 (4 minutes 31 seconds and 4 minutes 18 seconds, $p < 0.05$); however, there was no significant difference between groups 1 and 2 ($p > 0.05$).

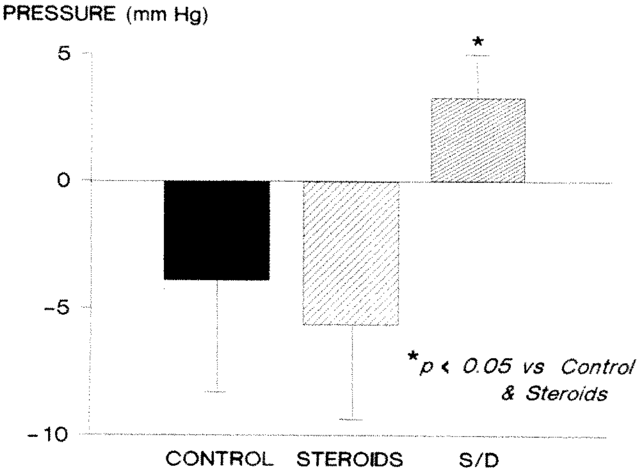

Fig 2. Comparison of mean spinal cord perfusion pressures of control group, steroid group, and group with steroids plus cerebrospinal fluid drainage (S/D).

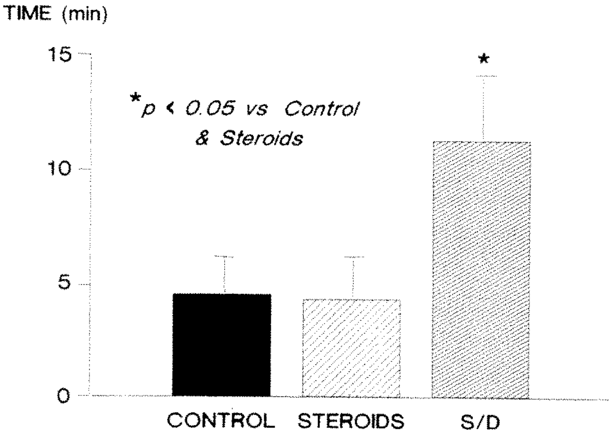

Fig 4. Comparison of time required for somatosensory evoked potential loss of control group, steroid group, and group with steroids plus cerebrospinal fluid drainage (S/D).

Comment

Paraplegia remains one of the most dreadful and unpredictable complications of operations on the thoracic and thoracoabdominal aorta. The etiology of paraplegia is multifactorial and includes prolonged duration of ischemia, interruption of critical intercostal arteries, sustained periods of hypotension, associated aortic dissection, and increases in CSFP with consequent decrease in SCPP [12, 15].

Spinal cord perfusion pressure is defined as the difference between D-BP and CSFP. To maintain a satisfactory SCPP, some investigators have tried to provide a high distal perfusion pressure with shunts and bypasses; however, these methods have not been uniformly successful and, for technical reasons, cannot be used to maintain adequate distal aortic perfusion in patients with extensive thoracoabdominal aneurysms [15]. Therefore, other investigators have concentrated on modulating the other determinant of SCPP—CSFP—and have shown experimentally and clinically that CSFD decreases CSFP and improves SCPP, thereby decreasing the incidence of postoperative paraplegia after cross-clamping of the thoracic aorta [4, 12].

Inherent to cross-clamping of the thoracic aorta is the occurrence of central hypertension, which must be controlled to avoid its deleterious effects on the myocardium and brain. Sodium nitroprusside has been and continues to be the most widely used agent for control of central hypertension during aortic operations, but recent evidence suggests that SNP causes a significant increase in CSFP, as well as a significant decrease in D-BP, thus reducing SCPP and compromising spinal cord blood flow [16].

Recently, we used CSFD to counteract the increase in CSFP caused by SNP and showed that CSFD only transiently ablates the increase in CSFP observed with SNP. The initial removal of a large amount of cerebrospinal fluid before aortic cross-clamping counteracts the initial cord expansion in the spinal canal. With time, resistance to further drainage of cerebrospinal fluid in the presence of increasing CSFP clearly shows that it is the loss of compliance of the spinal canal from edema of the cord, not an increase in cerebrospinal fluid production, that causes the increase in CSFP [6].

Steroids have protective effects during spinal cord ischemia because they act as free radical scavengers and membrane stabilizers and have antiedema effects [8–10]. Therefore, we investigated the role of steroids in association with CSFD to protect the spinal cord during aortic cross-clamping when SNP and partial exsanguination are used to control proximal hypertension.

In this study, use of partial exsanguination (40% of estimated blood volume) before aortic cross-clamping reduced the total amount of SNP required to control P-BP and facilitated the control of blood pressure to values more comparable with those desired in clinical practice. In the present study, CSFP did not increase after aortic cross-clamping, in contrast to our previous study [3], in which SNP significantly increased CSFP; maintenance of a higher mean P-BP (100 mm Hg) and the increased amount of SNP required in that study could explain the difference. However, we have documented that SNP increases CSFP, though to a lesser degree, even when a mean P-BP of 80 mm Hg is maintained (unpublished observations). We therefore believe that absence of a CSFP increase in the present study was related to use of exsanguination. Partial exsanguination may prevent the increase in CSFP observed when SNP is infused during aortic cross-clamping; this may occur because partial exsanguination decreases the intravascular blood volume and may decrease spinal cord edema. Nevertheless, SNP induces loss of autoregulation of spinal cord blood flow [16] that cannot be prevented by steroids or CSFD or a combination of the two.

Steroids did not reduce CSFP in group 2 (10.7 versus 14.2 mm Hg, $p > 0.05$) but enabled successful reduction of CSFP by CSFD in group 3. Of greater importance in this group, CSFP could be maintained at near zero levels throughout the cross-clamp interval, whereas this could not be accomplished by CSFD in our previous study. Because we did not use steroids and CSFD in a group in which P-BP was controlled with SNP alone, we cannot isolate the factor (steroids or exsanguination) responsible for the prolonged reduction of CSFP.

Steroids alone appeared to have some protective effect on the spinal cord in the presence of negative SCPP: 4 of 7 animals in this group did not suffer neurological injury. There was no statistical difference, however, between the steroid-treated group and untreated controls (4 of 7 versus 5 of 6 injured, $p < 0.05$). This differs from the results of Laschinger and co-workers [7], which showed that all steroid-treated animals had complete recovery after an 18.33-minute ischemic interval. The shorter duration of warm ischemia with a higher P-BP (120 to 140 mm Hg) may account for the different results. A higher P-BP implies a higher D-BP, hence a better SCPP. Because less SNP may have been required to maintain a mean P-BP of 120 to 140 mm Hg, the detrimental effects of SNP may have not been apparent.

Our results showed that 7 of 9 animals with positive SCPP were neurologically intact; in contrast, only 3 of 10 animals with negative SCPP were intact postoperatively ($p < 0.05$). The two paralyzed animals in the group with positive SCPP had pressures ranging from 5 to 10 mm Hg; paradoxically, the remaining 7 uninjured animals had SCPPs ranging from 0 to 5 mm Hg.

In a previous study [12], we showed that an SCPP of 10 mm Hg was the threshold value for maintaining spinal cord integrity for a 40-minute cross-clamp interval, and with a shorter cross-clamp of 30 minutes SCPP as low as 2.3 mm Hg was associated with spinal cord integrity. In the present study, 3 animals with negative SCPP scored Tarlov grade 3 (unsteady gait), in contrast to our previous observations. None of the animals with negative SCPPs had complete neurological recovery (Tarlov grade 4). Based on the present findings regarding SCPP, as it relates to postoperative neurological outcome, a critical threshold of SCPP appears not to be an absolute error-free measurement. We believe that the individual variability may be based on the degree and type of collateralization, which cannot be properly measured by SCPP alone.

Paraplegia results from spinal cord ischemia, which in turn is caused by inadequate spinal cord blood flow: spinal cord blood flow as low as 4 mL/100 g per minute may prevent neurological injury in primates [17]. Monitoring techniques that yield on-line information on spinal cord blood flow are needed, because they will enable prediction of neurological outcome without error. Measurement of SCPP is now the only available method of assessing spinal cord blood flow indirectly.

Spastic paraplegia developed in 2 of 9 animals with positive SCPP postoperatively. This corroborates clinical findings reported by Crawford and associates [18] that showed that patients with high distal aortic pressure (80 to 116 mm Hg) while on bypass, at flow rates less than 2,000 mL per minute, had a high incidence of paraplegia. We must identify the role of regional vascular resistance and the factors affecting it to understand why high SCPPs do not always generate the spinal cord blood flow required to prevent paraplegia.

As in a previous study [7], we confirmed that time to SEP loss is not an accurate predictor of neurological outcome in animals treated with steroids. Loss of SEP in the group treated by steroids alone occurred at a time similar to that of controls (4 minutes 18 seconds versus 4 minutes 31 seconds, $p > 0.05$); however, although all control animals were paralyzed, 4 of 7 steroid-treated animals were spared neurological injury. Animals with loss of electrophysiological conduction of the spinal cord at a statistically significant later time (group 3 versus groups 1 and 2, 11 minutes 16 seconds versus 4 minutes 18 seconds and 4 minutes 31 seconds, $p < 0.05$) had a better neurological outcome. This study shows that SEP loss occurring later, independent of treatment, is more predictive of neurological outcome than an early loss occurring in animals treated with steroids.

Based on the results of the present study, we believe that in cases in which mechanical control of central hypertension cannot be achieved for either anatomical or technical reasons and in which SNP or any other nitrate vasodilators must be used, steroids in conjunction with cerebrospinal fluid drainage may provide better spinal cord protection than either treatment alone. At present we are unable to identify an intrinsic protective role of partial exsanguination, but we can infer that exsanguination may mitigate the deleterious effect of SNP on SCPP by decreasing the amount of SNP required to control proximal hypertension in a canine model. Further studies are required to elucidate the effects of partial exsanguination on hemodynamics and cerebrospinal fluid dynamics.

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DISCUSSION

DR DENTON A. COOLEY (Houston, TX): I've enjoyed hearing this paper and the paper by Svensson and associates [1] and I think they are certainly very important. Some of them bring back memories of the work we did more than 20 years ago with spinal fluid drainage.

From a practical standpoint, one wonders whether this work is worthwhile. I hope it does not get into the literature that CSFD is going to be consistently protective in this problem of paraplegia, which is not only a medical problem but has become a serious legal problem for the clinical surgeon.

Dr Blaisdell and I used spinal cord drainage clinically in a small series of patients in the past and found very little effect. Another problem was the high incidence of serious spinal headaches after use of this technique. That was a disabling feature.

In our own laboratory, we have tried to do some local hypothermic experiments in animals. Dr Rolondo Colon had a very interesting paper recently in which he tried to segmentally cool the spinal cord during periods of cross-clamping. It was very effective. I am sure that all cardiovascular surgeons are impressed with the excellent results that have been achieved by inducing general body hypothermia for cerebral protection during arch replacement. Hopefully we could use this technique in protecting the rest of the central nervous system, namely, the spinal cord.

It is not often practical to try to reimplant segmental vessels. There may be no patent segmental vessels visible.

All methods of protecting against paraplegia are interesting, but the problem is far from solved. No method yet developed gives complete and dependable prevention of paraplegia in extensive resection of the distal thoracic aorta.

DR WOLOSZYN: Thank you, Dr Cooley, for bringing to our attention all of the stated facts.

We do not want to give the impression that this is a cure-all. What we are looking for is a combined modality approach to prolong warm ischemia, and by doing separate animal studies, we may be able to isolate different factors that will influence postoperative paraplegia rates.

The fact that CSFD has little effect on the outcome of postoperative paraplegia is noted, and it is indeed true. Our intention was to show that drainage is effective if proximal hypertension is not controlled, whereas when the proximal hypertension or central hypertension is controlled with pharmacological agents, specifically the nitrate vasodilators (Nipride), that some of its deleterious effects may be mitigated by CSFD. Drainage alone is not effective, but when combined with steroid administration it may indeed prove beneficial, although not uniformly protective. Other methods will need to supplement this to eventually prevent paraplegia after thoracic aortic cross-clamping.

Your second comment on profound hypothermic arrest is indeed interesting. It has been shown that hypothermic arrest is beneficial for maintaining cerebral neurological status. It has not shown any benefit for the spinal cord unless it is administered through the intrathecal space.

Third, your mention of reimplanting the critical intercostal vessels is absolutely essential, as illustrated in the paper by Svensson and associates.

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Ten-Year Experience With Aortic Valve Replacement in 482 Patients 70 Years of Age or Older: Operative Risk and Long-Term Results

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A retrospective analysis of an institutional experience with aortic valve replacement (AVR) in patients 70 years of age or older during 1976 to 1987 was performed. The study was prompted in part by the current interest in palliative aortic valvoplasty, an interest based to a certain extent on the impression that AVR in the elderly has a high mortality. The mean age of the patients was 75.0 ± 4.0 years (± the standard deviation) (range, 70 to 89 years). Eighty-three percent of patients received porcine valves and 17%, mechanical valves. Preoperatively 32% were in New York Heart Association class III, and 59% were in class IV. Operative mortality was 5.6% for elective isolated AVR for aortic stenosis (19% of all patients), 8.2% for all isolated AVR (38%), and 12.4% overall. Concomitant operative procedures were done in 62.0%; AVR with coronary artery bypass grafting (42%) had an operative mortality of 14.3%. Multivariate analysis showed significant predictors of operative mortality to be emergency operation ($p < 0.01$), isolated aortic regurgitation ($p = 0.01$), and previous cardiac operation ($p = 0.02$). Follow-up (34 ± 27 months) was 94% complete. Five-year survival from late cardiac-related death was 81.0%. The constant yearly hazard rate for late death for patients 70 years of age or older who underwent AVR was 5.42% per year, which is similar to the 5.77% per year rate calculated for age-matched and sex-matched controls. Five-year freedom from reoperation was 99%; from late thromboembolic complications, 91%; and from late anticoagulant-related complications, 94%. Freedom from all valve-related morbidity and mortality was 61% at 5 years. At follow-up, 80% of patients reported symptomatic improvement, and 76% were in New York Heart Association class I or II. These results show that AVR in the elderly is safe and effective, with late survival rates similar to those of the general population. Thus AVR remains the procedure of choice in patients 70 years of age or older with substantial aortic valve disease.

(Ann Thorac Surg 1990;49:84–93)

Recent interest in aortic balloon valvoplasty [1, 2] has been based in part on the impression that aortic valve replacement (AVR) in the elderly has a high operative mortality [1, 3]. The results of aortic valvoplasty, however, currently must be viewed as palliative at best because the 6-month mortality after this procedure is in the range of 10% to 20% and the 6-month rate of restenosis approaches 50% [1, 2]. In contrast, many centers have now published operative mortality rates of less than 10% for AVR in the elderly population [4–10] along with excellent long-term survival rates [6–12].

Cold blood potassium cardioplegia was introduced for intraoperative myocardial protection at New York University Medical Center in 1976. Because of our confidence in this technique, we have not considered diminished left ventricular function to be a contraindication to operation. Likewise, advanced age has not been an operative contraindication. This retrospective review of our institutional experience with AVR in patients 70 years of age or older was performed to document the results of surgical therapy in this patient population and to identify the incremental risk factors predictive of poor operative and long-term outcomes.

Material and Methods

Basic Characteristics of the Study Group

This study examined hospital and follow-up data on 482 consecutive patients 70 years of age or older who underwent AVR at New York University Medical Center between 1976 and 1987. Fifty-five percent were male, and 45% were female. The mean age at operation was 75 ± 4 years (± the standard deviation) (range, 70 to 89 years).

The vast majority of patients (83%) received a porcine valve prosthesis, but 17% were selected to receive a mechanical prosthesis. Thirty-eight percent (183 patients) underwent AVR as an isolated procedure, whereas 62% (299 patients) had AVR plus a concomitant operative procedure. These concomitant procedures included coronary artery bypass grafting in 42% (203) of all patients, mitral valve replacement or repair in 15% (71), tricuspid valve operation in 2% (8), and other procedures in 10%

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Table 1. Analysis of Risk Factors Associated With Operative Mortality in Aortic Valve Replacement in 482 Patients 70 Years Old or Older[a]

Risk Factor	Univariate Analysis (χ^2)	Multivariate Analysis (Odds Ratio)[b]
Emergency operation	12.05 (<0.01)	3.80 (<0.01)
Isolated aortic regurgitation	8.56 (<0.01)	3.21 (0.01)
Previous cardiac operation	. . . (NS)	2.17 (0.02)
Concomitant cardiac procedure	4.89 (0.02)	. . . (NS)
Mean pulmonary artery pressure ≥ 30 mm Hg	3.66 (0.06)	. . . (NS)
Systolic pulmonary artery pressure ≥ 60 mm Hg	. . . (NS)	. . . (NS)
Age	. . . (NS)	. . . (NS)
Type of prosthesis	. . . (NS)	. . . (NS)
Concomitant bypass grafting	. . . (NS)	. . . (NS)
NYHA class	. . . (NS)	. . . (NS)
Sex	. . . (NS)	. . . (NS)
Cardiac index < 2 L/min/m^2	. . . (NS)	. . . (NS)
Body surface area ≤ 1.8 m^2	. . . (NS)	. . . (NS)
LVEDP ≥ 25 mm Hg	. . . (NS)	. . . (NS)
Peak aortic gradient ≥ 75 mm Hg	. . . (NS)	. . . (NS)

[a] Data in parentheses are p values. A p value of greater than 0.05 was not significant. [b] Stepwise logistic regression was used.

LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association; NS = not significant.

(50). Preoperatively, 9% of the patients were in New York Heart Association (NYHA) class II, 32% were in NYHA class III, and 59% were in NYHA class IV. Eighty-seven percent of all patients underwent a primary elective operation, 4% had a reoperative elective operation, and 9% required an emergency operation for hemodynamic deterioration.

The preoperative diagnosis of the predominant valvular lesion was aortic stenosis in 49% of all patients, mixed stenosis and insufficiency in 24%, aortic insufficiency in 17%, prosthetic valve dysfunction in 2%, and undetermined in 7%. The mean peak aortic valve gradient in patients with aortic stenosis, with or without aortic insufficiency, was 70.5 ± 29.4 mm Hg.

Operative Technique

All patients were operated on using cardiopulmonary bypass with the DeBakey roller pump and moderate systemic hypothermia (core temperature, 25° to 30°C). Operations were done with a single period of aortic cross-clamping using multiple doses of cold blood potassium cardioplegia (6° to 10°C) for myocardial protection. Direct coronary ostial injection with close monitoring of injection pressure was used for most patients. A thermistor probe was used to monitor myocardial cooling, and blood cardioplegia was administered until the myocardial temperature reached 8° to 12°C. Topical cooling was also used; the heart was wrapped with a laparotomy pad, and the pericardium was continuously irrigated with cold saline solution, which diminished the rate of myocardial rewarming. Cardioplegic solution was reinjected every 20 to 30 minutes as necessary. This protection technique is described in some detail, as it may be largely responsible for the good results reported. With this method of myocardial protection, a myocardial temperature of less than 15°C can be maintained for long periods, and thus excellent myocardial protection can be achieved even during a prolonged period of aortic cross-clamping.

All aortic valvular tissue was excised, and calcium was removed from the surrounding annulus with a rongeur when necessary. Care was routinely taken to pack the left ventricular cavity with a gauze pad during the debridement of calcium from the annulus. The annulus and left ventricular cavity were irrigated copiously with saline solution by means of a bulb syringe, and the gauze pack was removed before the seating of the valve. This simple maneuver has proved extremely effective in minimizing the risk of embolization.

More important, in recent years a long aortic-arch cannula was passed beyond the arch vessels whenever calcium was palpable in the ascending aorta or in the aortic arch. Early experience with this technique has been

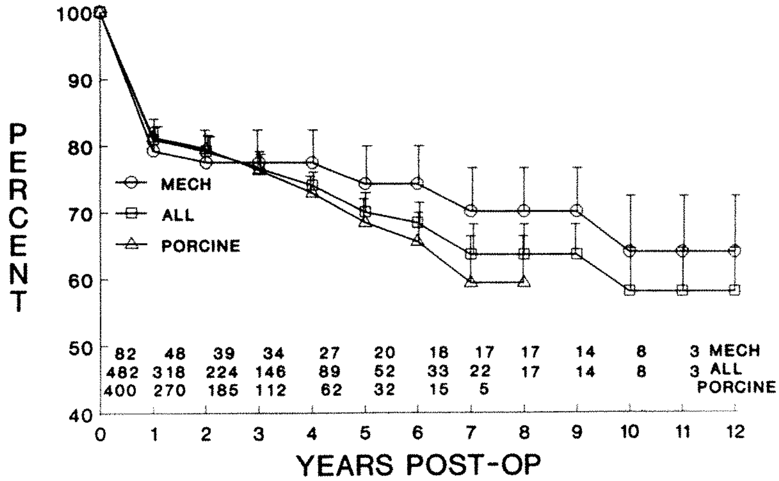
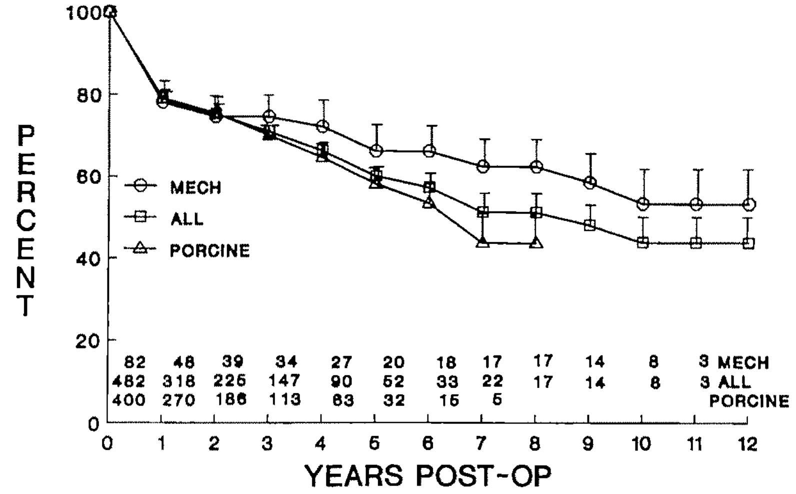


Fig 1. Actuarial freedom from all cardiac-related death after aortic valve replacement in patients 70 years of age or older. (MECH = mechanical.)

Fig 2. Actuarial freedom from all death after aortic valve replacement in patients 70 years of age or older. (MECH = mechanical.)



described by Culliford and colleagues [13]. In brief, the arch cannula is placed primarily to avoid the "sandblast" effect of a standard perfusion cannula on the undersurface of an atheromatous aortic arch. In our experience, embolization of atheromatous debris from the aortic arch is a frequent source of stroke when a standard aortic cannula is used in the elderly population. This can be avoided in most cases by use of the long aortic-arch cannula. Rarely, a brief period of circulatory arrest was necessary to perform suction endarterectomy of a densely calcified and atheromatous aortic arch, followed by placement of the aortic cross-clamp under direct vision. This more radical approach was reserved for patients with densely calcified aortic arch disease and is not necessary in most cases. Thus the key points in avoiding stroke are the frequent use of a long aortic-arch cannula and the routine packing and irrigation of the left ventricular cavity during valve removal.

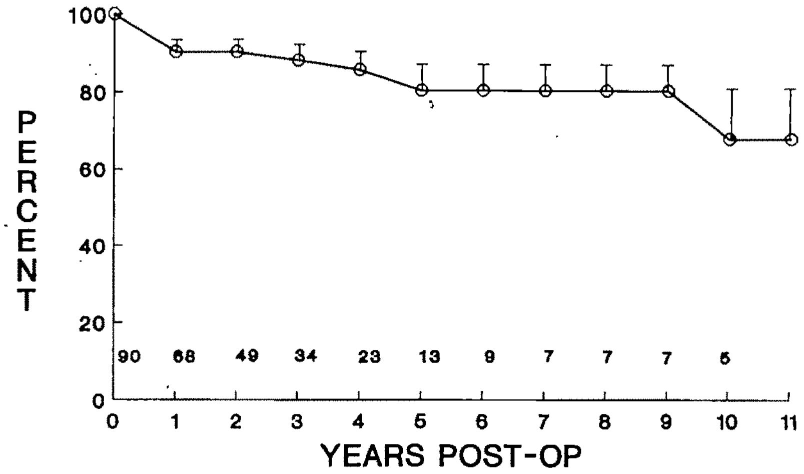
Aortic valves were inserted by means of a Teflon pledget–reinforced horizontal mattress suture technique, usually totaling 12 sutures. The oblique aortotomy incision was routinely closed with 4-0 continuous Prolene sutures (Ethicon, Somerville, NJ), although 5-0 Prolene was used when an exceptionally thin aorta was encountered.

Postoperatively, close attention was given to nutritional requirements, with careful daily tabulation of nitrogen balance and caloric intake. By the fourth postoperative day, most patients were receiving approximately 30 kcal/kg/day, with tube feeding or intravenous hyperalimentation as necessary. The importance of adequate nutrition cannot be overemphasized, as even short periods of starvation can prove to be extremely hazardous in the elderly patient population.

Anticoagulation

Select patients in the porcine AVR group were initially placed on a regimen of crystalline warfarin sodium (Coumadin) on the third postoperative day and continued on this therapy for a minimum of 3 months, whereas other porcine AVR patients received antiplatelet therapy only. All patients in the mechanical AVR group were maintained on a long-term regimen of warfarin with a desired prothrombin time 1.5 to 2 times the control level. Long-term care and anticoagulation therapy, however, were usually directed by the individual patient's primary phy-

Fig 3. Actuarial freedom from all death after elective isolated aortic valve replacement for pure aortic stenosis in patients 70 years of age or older.



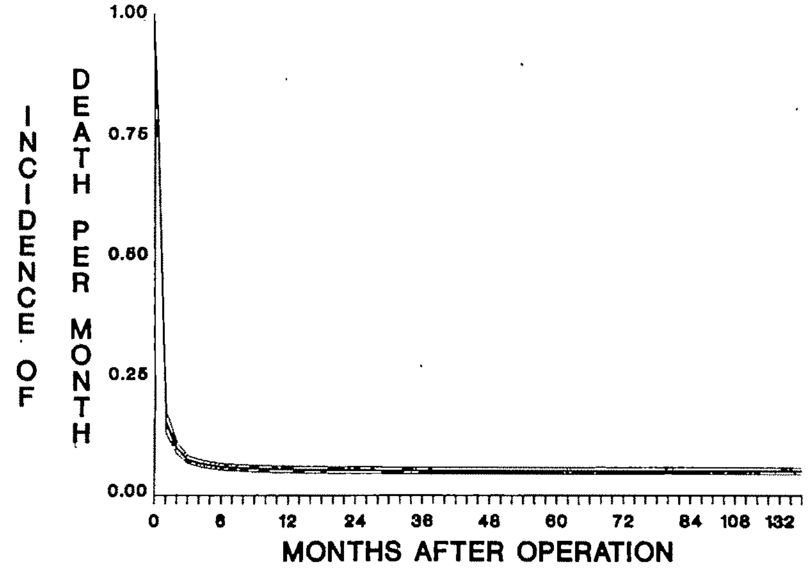


Fig 4. Hazard function for death in the first 12 years after aortic valve replacement in patients 70 years of age or older. The instantaneous risk of death is along the vertical axis, and the time after operation is along the horizontal axis. The broken lines *enclose the 95% confidence interval. There is an early phase of rapidly falling risk and a constant phase that extends throughout follow-up.*

sician. Of the porcine AVR group, 27.1% were on a regimen of warfarin, 72.3% were receiving antiplatelet therapy only, and 0.6% were not receiving any anticoagulation or antiplatelet therapy at the time of follow-up. Of the mechanical AVR patients at follow-up, 97.5% were receiving warfarin and 2.4% were receiving antiplatelet therapy only.

Follow-up Data

Follow-up information was obtained directly from the patient at the time of a follow-up office visit or by telephone interview with the patient, the patient's physician, or both, and was 94% complete. The mean follow-up was 33.9 ± 27.4 months (range, 1 to 144 months; total, 1,121 patient-years). If the cause of any death could not be determined because it occurred suddenly, outside the hospital, or without postmortem examination, the death was classified as cardiac related. The methods used for classifying valve-related morbidity and mortality conformed to the guidelines proposed by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity [14].

Data and Statistical Analysis

This study provided for the analysis of 150 or more specific data points for each patient. Preoperative and perioperative data were obtained by reviewing the patient's hospital record. All data were entered into a computer and analyzed by means of the statistical software packages SPSS^x (SPSS Inc, Chicago, IL) or SAS (SAS Institute Inc, Cary, NC). All results are expressed as the mean ± one standard deviation except as otherwise indicated. Analysis of the significance of differences in preoperative and postoperative characteristics was performed by χ^2 analysis or Student's t test as appropriate. Actuarial curves for mortality or late complications were obtained by the life-table method, and the overall significance of difference between groups was determined by the approach of Lee and Desu [15]. Multivariate analysis of factors that might affect hospital mortality was performed by stepwise logistic regression analysis. Multivariate analysis concerning time-related events was accomplished by hazard function analysis [16, 17]. In some analyses, the parametric survivorship function was used to calculate the probability of an event occurring within any time period.

Table 2. Hazard Function Analysis of Survival From All Death With Concomitant Risk Factor Information in Patients 70 Years Old or Older With Aortic Valve Replacement (Two-Phase Model)[a]

Risk Factor	Parameter Estimate
Early phase	
Emergency operation	1.23 (<0.001)
Isolated aortic regurgitation	0.75 (<0.001)
Concomitant cardiac procedure	0.70 (0.01)
Constant phase	
Peak aortic gradient ≥ 75 mm Hg	−0.97 (0.03)
NYHA class	0.49 (0.04)

[a] Data in parentheses are p values.

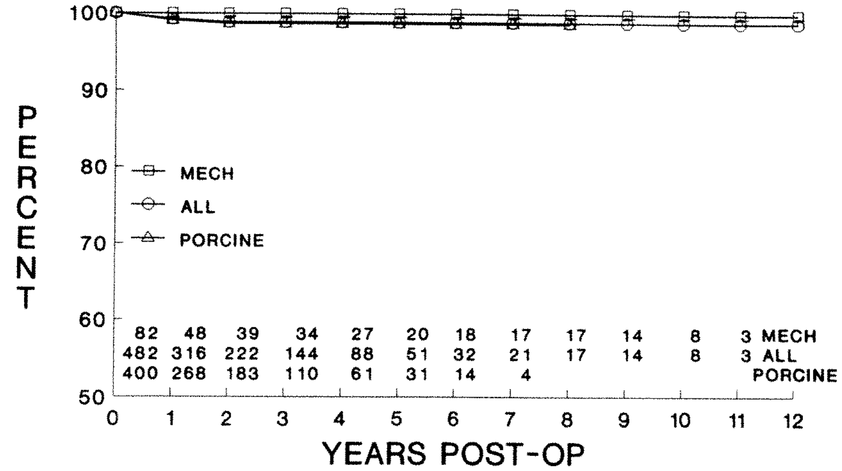
NYHA = New York Heart Association.

Table 3. Comparison of New York University Patient Group With Age-Matched and Sex-Matched Controls From the General Population

Group	Hazard Rate for All Deaths (deaths/yr)	Calculated 5-Year Survival (% survival)
NYU group	0.0542	75.7
Census controls	0.0577	74.3

NYU = New York University.

Fig 5. Actuarial freedom from any reoperation on the aortic valve or aortic valve failure after aortic valve replacement in patients 70 years of age or older. (MECH = *mechanical.*)



Results

Early Results

OPERATIVE MORTALITY. The operative mortality for patients having elective isolated AVR for pure aortic stenosis was 5.6%. Mortality for all isolated AVR was 8.2%, and AVR with concomitant coronary artery bypass grafting had a mortality of 14.3%. The overall operative mortality was 12.4%.

The factors predictive of increased operative risk as determined by multivariate logistic regression analysis were emergency operation ($p < 0.01$), isolated aortic regurgitation ($p = 0.01$), and history of a previous cardiac surgical procedure ($p = 0.02$). All risk factors analyzed for association with operative mortality and their respective p values are displayed in Table 1.

PERIOPERATIVE COMPLICATIONS. The incidence of perioperative complications was surprisingly low in view of the advanced age of the patient population. Stroke occurred in only 2.7%, 1.9% had sternal infections, 2.7% sustained a myocardial infarction, 4.8% required prolonged ($\geq$7 days) respiratory support, and 7% had low cardiac output syndrome.

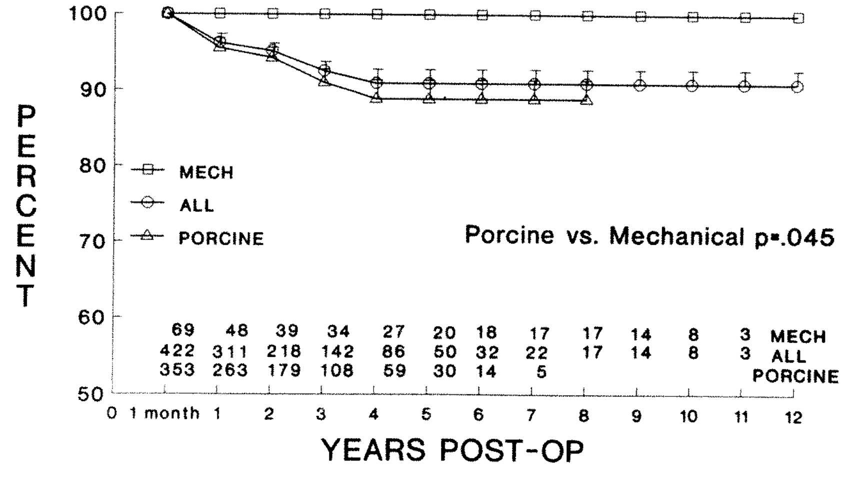
Late Results

SURVIVAL. The overall actuarial freedom from all cardiac-related death was 81.0% at 1 year and 70.0% at 5 years (Fig 1). The overall freedom from all death (hospital or late, cardiac related or noncardiac related) was 79.0% at 1 year and 60.0% at 5 years (Fig 2). However, the overall 1-year and 5-year survivals for elective isolated AVR for pure aortic stenosis were 90.4% and 80.6%, respectively (Fig 3). No significant differences could be detected between the porcine and mechanical AVR patient groups for any of the survival results.

Figure 4 depicts the early and late hazard phases for risk of death with time zero beginning at the start of the operative procedure. The classic biphasic hazard-risk curve described by Blackstone and Kirklin [16, 17] was noted. Hazard function analysis for incremental risk factors revealed that emergency operation, isolated aortic regurgitation, and concomitant cardiac procedures were the incremental risk factors in the early hazard phase (Table 2). These are similar to the perioperative risk factors identified by stepwise logistic regression analysis (see Table 1). The incremental risk factors identified in the late constant phase of the hazard function analysis were NYHA functional class as a predictor of diminished survival and peak aortic valve gradient of 75 mm Hg or higher as a predictor of improved survival (see Table 2).

When the constant hazard rate for late death was compared with the yearly hazard rate for death in age-matched and sex-matched controls from the general population (Table 3) [18], the results showed that the yearly

Fig 6. Actuarial freedom from late thromboembolic complications after aortic valve replacement in patients 70 years of age or older. (MECH = *mechanical.*)



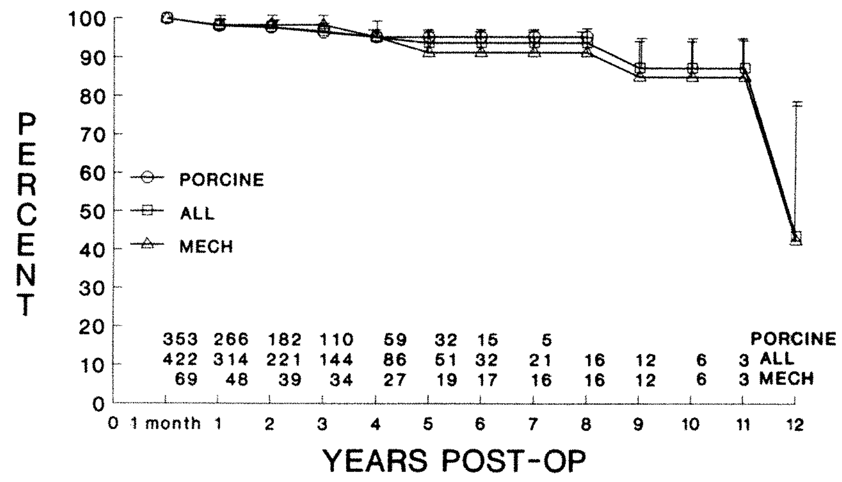


Fig 7. Actuarial freedom from late anticoagulant-related complications after aortic valve replacement in patients 70 years of age or older. (MECH = mechanical.)

risk of death in hospital survivors among patients 70 years of age or older who underwent AVR is similar to that noted in the general population control (5.42%/year versus 5.77%/year). Using this hazard rate, the projected 5-year survival in such hospital survivors is 76% compared with an expected 5-year survival of 74% in age-matched and sex-matched controls from the general population.

FUNCTIONAL IMPROVEMENT. At follow-up, 87.7% of surviving patients reported symptomatic improvement. Seventy-six percent of the operative survivors were found to be in NYHA functional class I or II, 22% were in NYHA class III, and 2% were in NYHA class IV.

LATE COMPLICATIONS. The actuarial 5-year freedom from reoperation was 99% (Fig 5). Ninety-one percent of the patients remained free from thromboembolism (Fig 6), 94% were free from anticoagulant-related complications (Fig 7), and 97% remained free from endocarditis (Fig 8) at 5 years. Thus late complications were less frequent than expected with 83% of the patients remaining free from all valve-related morbidity at 5 years (Table 4), and 61% of the patients remaining free from all valve-related morbidity and mortality at 5 years (Fig 9; see Table 4). Morbidity was not significantly different between those who received porcine valves (n = 400) and those who received mechanical valves (n = 82) (see Table 4).

Comment

The low operative mortality reported here of 5.6% for elective AVR for aortic stenosis, 8.2% for all isolated AVR, and 12.4% overall for AVR in patients 70 years of age or older is similar to that in several reports [6–11] and more encouraging than in others [3, 12]. Overall, the incremental risk factors predictive of operative risk by parametric analysis were emergency operation, the presence of isolated aortic regurgitation, and the performance of concomitant cardiac procedures.

The factor in the operative technique most likely to be responsible for the low operative mortality reported is the careful attention paid to intraoperative myocardial protection. Low cardiac output syndrome necessitating substantial pressure support occurred in only 7% of the patients. Likewise, the 5-year freedom from all cardiac-related

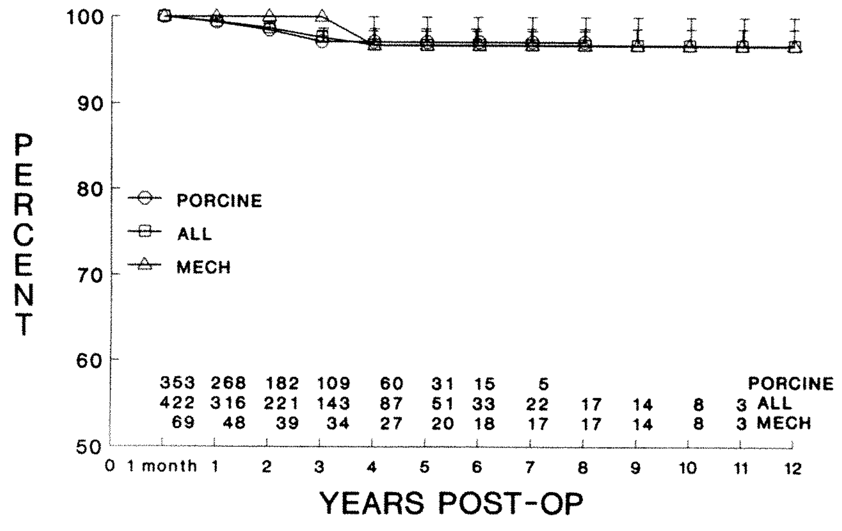


Fig 8. Actuarial freedom from late endocarditis after aortic valve replacement in patients 70 years of age or older. (MECH = mechanical.)

death was 70%, thus further emphasizing the value of excellent myocardial preservation. The need for optimal myocardial protection is most pronounced in the patient with a low cardiac index or pulmonary hypertension because such patients often have long-standing valvular heart disease with deteriorating left ventricular function. In this report, the presence of a low cardiac index or the presence of major pulmonary hypertension did not adversely affect operative risk or late survival, further demonstrating the value of the myocardial protection strategy used.

Clearly the risk of stroke is of great concern when elderly patients undergo operation. Craver and associates [6] reported a 5.3% incidence of stroke after AVR and a 10.8% incidence of stroke after AVR plus coronary artery bypass grafting in patients 70 years of age or older. In contrast, the low overall incidence of stroke reported here (2.7%) is quite encouraging and appears to be at least in part due to judicious use of left ventricular packing to avoid the spillage of calcium fragments and due to frequent use of the long aortic-arch cannula to avoid aortic arch embolization. These important points in the operative technique are invaluable aids in minimizing the risk of stroke.

The risk of late death of 5.4% per year among operative survivors is surprising inasmuch as it is roughly equivalent to the yearly risk of death in the age-matched and sex-matched general population. Certainly poor NYHA functional classification had a negative effect on late survival, but the generation of a high gradient (≥75 mm Hg) across the aortic stenosis conferred a strongly positive effect on late survival.

In view of the excellent results reported here and elsewhere, the proper role of aortic valvoplasty in the elderly population appears to remain a limited one. In recent years, enthusiastic reports [1, 19, 20] have supported the widespread use of balloon valvoplasty to correct aortic stenosis, especially in subgroups of patients such as the elderly in whom the operative mortality was allegedly excessive. The hospital mortality for such aortic valvoplasty procedures has ranged from 3% to 8% [21, 22]. More recently, however, longer-term studies have shown actuarial 1-year survival after aortic valvoplasty to be poor [23] and severe restenosis within 3 to 18 months of aortic valvoplasty to be virtually inevitable [24–26]. As the results of the present study demonstrate, elective isolated AVR for pure aortic stenosis in patients 70 years of age or older has a hospital mortality equivalent to that noted for balloon valvoplasty and has 1-year and 5-year survivals of 90.4% and 80.6%, respectively. Furthermore, the data indicate that restenosis or reoperation are not pertinent issues with AVR in the elderly. Therefore, aortic balloon valvoplasty should not be considered a valid alternative to AVR in most older patients with aortic stenosis. In general, balloon valvoplasty is appropriate only for a very select patient population, and the more definitive AVR procedure should be used whenever possible.

In conclusion, AVR has proved to be safe and effective in the elderly population and should be considered the

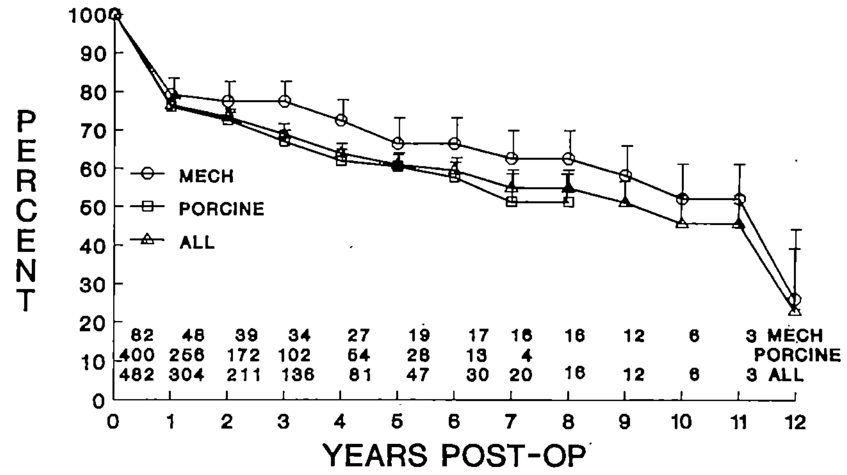
Table 4. Five-Year Freedom From Late Complications for Patients 70 Years Old or Older With Aortic Valve Replacement

Complication	Porcine (%)	Mechanical (%)	Overall (%)	p Value[a]
Thromboembolism	88.9	100	91.0	0.045
Anticoagulant-related complication	95.2	91.1	93.6	NS
Endocarditis	97.1	96.8	96.8	NS
Reoperation or valve failure	98.7	100	98.9	NS
Freedom from all above valve-related morbidity	83.3	88.3	83.3	NS
Freedom from all valve-related morbidity and mortality	60.6	66.5	61.1	NS

[a] A p value of greater than 0.05 was not significant.

NS = not significant.

Fig 9. Actuarial freedom from all cardiac-related morbidity and mortality after aortic valve replacement in patients 70 years of age or older. (MECH = mechanical.)



procedure of choice for most elderly patients with aortic valve disease.

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DISCUSSION

DR DAVID ALAN OTT (Houston, TX): I congratulate Galloway and associates on this well-documented report, which comes at a critical time in the evolution of the treatment of aortic valve disease.

I have shown Dr Galloway our confirmatory evidence that the risk of AVR in the elderly is acceptable. I would ask him to comment, because although perhaps these figures are not statistically significant for the different age groups, certainly we think there is a trend toward a higher mortality in the older patients. In our patients the 5-year survival in the elderly patient undergoing AVR is similar to that of age-matched controls.

We were privileged to see a paper in preparation from Dr Terry Ferguson and our cardiology group indicating that balloon dilation of the aortic valve at our institution is associated with a fairly low immediate risk. However, the 1-year mortality is 30%, and another 20% of those patients who underwent balloon valvotomy required aortic valve replacement within one year. Interestingly, none of those patients who required AVR after recurrence died after operation. This is in keeping with data from other institutions. If we review the most recent data, it specifically indicates that in many institutions the mortality of balloon valvotomy is equal to or even greater than the immediate operative mortality, that the restenosis rate within 1 year is 40% to 50%, and that the 1-year survival rate is only 70% to 75%, whereas the 5-year survival rate after AVR is 70% to 75%.

We think the evidence is definitive that the role of balloon valvotomy is a very limited one, and that balloon valvotomy should be reserved only for the most cachetic, senile, or preterminal patients and a few other specific situations. This is not surprising in view of the fact that the mean valve area after balloon valvotomy is less than 1 cm, whereas the valve orifice of the commonly used bileaflet disc valve is 3 cm in the 25-mm size.

As usual, we have to take some risk at the time of operation for a good long-term result, but most patients are best served by that method.

DR KIT V. AROM (Minneapolis, MN): I support the findings from the New York University group, sharing the same concern about palliative aortic valve dilation in the elderly. We recently looked at our experience at the Minneapolis Heart Institute. Two hundred seventy-three patients underwent AVR using the St. Jude Medical prosthesis during a 10-year period starting in 1978. The main indication for operation was severe congestive heart failure regardless of the degree of severity of left ventricular function. The mean age was 75 years. There were 162 AVRs and 111 AVRs combined with coronary artery bypass grafting (CABG). The operative mortality was 5%, which included deaths within 30 days after operation or deaths occurring during the same admission. The operative mortality for AVR alone was 6%, and it was only 3.6% for AVR and CABG.

Ninety-six percent of the patients were contacted for follow-up. The mean follow-up was 33.4 months, for a total of 9,130 patient-months. The late mortality of the entire group was 18%: 20% in the AVR group and 14% in the group with AVR and CABG. There were no mechanical failures and a very low incidence of valve-related deaths and complications. Of those who survived, 98% were in functional class I and II, compared with 95% in functional class III and IV before operation.

The actuarial analysis showed that there was a high rate of freedom from thromboembolism (92.7% ± 4.1% for AVR and 94.3% ± 2.9% for AVR + CABG) and hemorrhagic complications (92.8% ± 3.8% for AVR and 97.3% ± 1.9% for AVR + CABG). The incidence of bleeding is surprisingly low even in these people who are elderly and receiving Coumadin. The rate of freedom from early death, valve-related death, and all complications was 56% in the group with AVR alone and 71% in the group with AVR and CABG.

As far as survival is concerned, if operative death is excluded, AVR alone had a 70% survival at 5 years; the rate for AVR and CABG was 78%.

We feel that AVR in the elderly has a low operative mortality. Long-term follow-up showed that 98% of the patients are now doing well. The procedure is safe and effective; the 5-year survival rate of these patients is close to that of the general population (74%) in a similar age group.

DR MANUEL J. ANTUNES (Coimbra, Portugal): I too wish to congratulate Galloway and colleagues for an excellent review and a well-presented paper clearly demonstrating both the safety and effectiveness of AVR in the elderly patient.

Our own experience in Johannesburg, South Africa, just published, concurs with that of Galloway and colleagues. In our study, which included about 400 elderly patients receiving mechanical valve prostheses (Medtronic-Hall or St. Jude) as an isolated procedure, the early mortality was only slightly but not significantly higher than that of the younger patients.

However, what was of importance was the incidence of thromboembolic events (1.8%/patient-year) and of anticoagulant-related hemorrhagic events (0.7%/patient-year), which were also comparable with those of younger patients. Furthermore, and this is most important, these valve-related complications were not of a greater severity in the elderly patients, which is in marked contrast with what is commonly believed. The mortality for all these complications related to anticoagulants, either in excess or in defect, is very low. Consequently, the 5-year survival with freedom from all valve-related complications was high, at 82%, while freedom from reoperation, which in my view is the most fearful complication in this group of patients, was 95%.

I believe that these results can be favorably compared with those of an identical series of tissue valve replacement and feel confident in the prediction that mechanical valves will prove to be a good alternative valve even for the elderly patient.

I have one question for Dr Galloway. Can you expand on your comparison of results between your mechanical and tissue valve groups, and explain your present policy?

DR YVES J. LOGEAIS (Rennes, France): We have recently reviewed our experience at the University of Rennes concerning operation for aortic stenosis during the last 13 years (1975 to 1988). Out of a total of 1,643 patients, 602 (36%) were 70 years old or older, and 67 (4%) were 80 years old or older. Of those 602 patients with mean age of 74.6 years, 60% were in NYHA class III or IV, and one third had associated diseases.

Bioprostheses were used in 77%. Different types of associated surgical procedures were performed (left ventricular outflow tract, 5%; ascending aorta, 4.6%). Associated CABG has been less frequent than in the series by Galloway and associates (7%).

The overall early mortality of the whole group was 11.4%, but for elective isolated AVR it was 10.4%. The only predictive factors of early death were functional class IV and age. It is interesting to note that within the group of elderly patients, age over 79 years was not a risk factor (six deaths out of 67 patients, or 8.9%), but at less than 70 years and 60 years the risk was very different (4.8% and 2.8%, respectively).

Follow-up has been 96.6% complete, with a mean of 3.6 years. Global survival at 5 years (including early mortality) is 67%, which is very close to the rate of 69% found by Galloway and associates, and the curve parallels that of the normal population of the same age.

There is no difference in survival between the groups with mechanical and biological prostheses, the two curves being exactly superimposed. Functional results have been excellent. Finally, in the group of octogenarians, results of operation are much better than those of balloon valvoplasty, which appear very disappointing. So, operation remains the treatment of choice of aortic stenosis even in very elderly patients, provided they are in satisfactory cerebral and general status.

DR BRADLEY J. HARLAN (Sacramento, CA): I congratulate Galloway and associates and support their conclusion. Their report stimulated my colleagues and I to look at our experience at Sutter Memorial Hospital, Sacramento, over the last 5½ years in this group of patients. This was a time frame in which valvoplasty was rarely performed at our hospital and very few patients were deemed unsuitable for surgical treatment. Of the 240 patients older than 70 years, I will concentrate on the 60 who were older than 80 years. In this subset of octogenarians, there was no mortality in 27 undergoing isolated AVR, 70% confidence limits of 0% to 3.6% mortality, and a 15.2% mortality in 33 patients undergoing AVR and CABG, with 70% confidence limits of 8.6% to 24.4%.

Advocating AVR in this group of patients to this audience is preaching to the choir. However, it is obviously important to have these data in the literature as the debate continues over the proper management of aortic stenosis in the elderly.

I have two questions for Dr Galloway. What was the incidence of aortic valvoplasty at NYU during the time frame of your study? Also, what do you consider at the present time to be appropriate use of aortic valvoplasty or dilation?

DR GALLOWAY: Certainly the collective series of the discussants further supports the contention that AVR is the treatment of choice for most patients over 70 years of age.

In response to Dr Ott's question, we did not find a progressive increase in mortality in patients 80 to 89 years of age. In fact, isolated AVR in those older than 80 years had a 3.6% mortality.

Most likely the differences in that trend versus the trend that you noted relates primarily to patient selection in that subgroup.

In response to Dr Harlan regarding the incidence of valvoplasty at NYU over the last 4 years, the cardiologists performed 50 valvoplasties at NYU over the past 4 years. By and large, that subgroup was completely different than our patients. About one third of the valvoplasty patients may have been good candidates for AVR, but the cardiac surgeons were not consulted. In the other two thirds the procedure was done in patients whose life expectancy was limited by cancer or some other associated disease. In a few patients the aortic pressure gradient was only 30 to 40 mm Hg and the cardiologists were not sure whether they were dealing with actual aortic stenosis or with cardiomyopathy; in these patients valvoplasty was done more for diagnostic purposes. I think this is kind of a weak indication. In my opinion valvoplasty should be considered only in bedridden, neurologically less than intact patients, or in patients in whom other diseases might substantially limit their life expectancy. Otherwise, patients that have a reasonable life expectancy and aortic stenosis should have AVR, as the data in this report indicate.

Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1992 may begin the recertification process in 1990. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1990. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Evolving Patterns in the Surgical Treatment of Malignant Ventricular Tachyarrhythmias

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The advent of the automatic implantable cardioverter defibrillator (AICD), generally viewed as a safe and effective intervention, has in some measure discouraged the use of electrophysiologically directed endocardial resection for intractable ventricular arrhythmias. We reviewed the records of 127 patients undergoing either AICD procedures or resection over a 6-year period. Thirty-day mortality was 5.6% (5/89 patients) for all AICD procedures, 10.7% (3/28) for AICD placement plus coronary artery bypass grafting, and 11.8% (4/34) for resection. These mortality figures are not significantly different. Patients undergoing resection were less likely to require antiarrhythmic agents than patients given an AICD (33% versus 61%). Survival at 2 years was 78% in the resection group and 72% in the AICD group. Survival at 4 years was still 78% in the resection group. Only 1 late sudden death occurred in the AICD group and none in the resection group. We conclude that resection continues to be a valuable alternative, offering a greater overall benefit at only slightly increased risk.

(Ann Thorac Surg 1990;49:94–100)

The direct surgical approach to ventricular arrhythmias began in 1978 with the introduction by Guiraudon and colleagues [1] of the encircling endocardial ventriculotomy and by Josephson and associates [2] of the subendocardial resection a year later. Since that time, experience with these techniques has accumulated at many centers. An elegant recent review and synthesis by Cox [3] compiles information on more than 800 patients treated by these direct surgical techniques at multiple institutions. A long-standing concern with these direct approaches aimed at eliminating the arrhythmia has been that they represent formidable operative procedures on patients who generally have sustained considerable prior myocardial damage from infarction. Operative mortality in most series has ranged from 10% to 20% [3].

After several years of testing, the automatic implantable cardioverter defibrillator (AICD) was approved for clinical use in the United States in 1986. Although the AICD represents only a palliative modality in the sense that the arrhythmia is accepted and corrected when it occurs, use of the device has burgeoned in the last several years. This popularity of the AICD is based on the perception that it is a safe and effective intervention, with an operative risk that is small compared with that of electrophysiologically directed arrhythmia procedures. The advent of the AICD has in some measure discouraged directed surgery for ventricular arrhythmias.

A number of reports [3–5] have begun to address the question of which patients should have electrophysiologically directed procedures and which should have an AICD placed. As no randomized comparisons of AICD placement versus electrophysiologically directed subendocardial resection are reported, this remains an open and important question.

We have continued to practice both directed resection and AICD placement. The choice has been individualized from patient to patient. The present study reviews retrospectively our experience over the past 6 years with the surgical treatment of malignant ventricular arrhythmias. The aim is to delineate the benefits and liabilities of the two methods—electrophysiologically directed resection and AICD placement—with an eye toward further clarifying clinical decision making. Because one of us (A.S.G.) moved from Yale University to Case Western Reserve University in August 1986, the experience reviewed here includes patients treated at both Yale-New Haven Hospital and University Hospitals of Cleveland.

Material and Methods

Patient Population

Case records were reviewed for all patients undergoing directed resection or AICD placement for ventricular arrhythmia. All were seen with cardiac arrest, syncope, or sustained ventricular tachycardia. A total of 127 patients were studied, 80 undergoing operation at Yale-New Haven Hospital between September 1983 and June 1989, and 47 undergoing operation at University Hospitals of Cleveland between September 1986 and June 1989. There were 99 male and 28 female patients ranging in age from 17 to 83 years with a mean age of 61.8 years. Nine patients were

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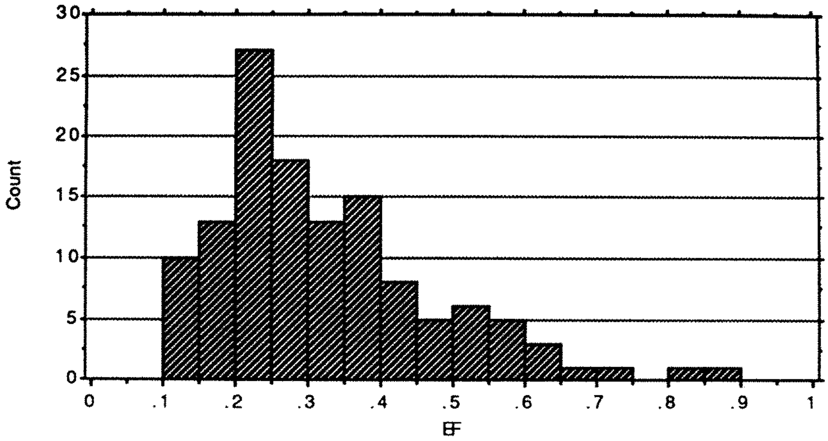

Fig 1. Ejection fraction (EF) for all patients. There was a concentration of patients in the range lower than 30%.

less than 40 years old, 6 were between 40 and 50 years old; 27, between 51 and 60 years old; 59, between 61 and 70 years old; 24, between 71 and 80 years old; and 2, older than 80 years.

The surgical procedure was endocardial resection in 34 and AICD placement in 89. Four patients had AICD patches alone and associated coronary artery bypass grafting (CABG). Of the 89 patients undergoing AICD placement, 61 had placement of the device alone and 28 had CABG in addition to AICD placement. Among the patients undergoing directed resection, 11 had resection alone, 13 had resection plus CABG, 6 had resection plus CABG plus AICD placement, and 4 had resection plus placement of the AICD.

All patients except those deemed in too unstable condition underwent electrophysiological evaluation before being referred for an arrhythmia procedure. Presenting symptoms were predominantly syncope (47 patients) or cardiac arrest (47 patients). Fifteen patients had palpitations as the presenting symptom, and 15 had other symptoms. Clinical rhythm was ventricular tachycardia (VT) in 75 patients and ventricular fibrillation (VF) in 45; it was unknown in 7. Etiology of the arrhythmia was related to coronary artery disease in 108 patients and to other causes in 19. Baseline preoperative electrophysiological study disclosed inducible arrhythmia in 113 patients, VT in 96 and VF in 17. In 14 patients, no arrhythmia could be induced at electrophysiological testing, despite clinical arrhythmic events.

Ejection fraction (EF) ranged from 10% to 88% with a mean of 31.5%. Sixty-eight patients had an EF less than 30%. The distribution of EFs is displayed in Figure 1.

Table 1 compares the clinical characteristics of the groups having AICD placement alone, AICD placement plus CABG, and directed resection. The mean EF was 34.7% in the AICD group, 31.2% in the AICD plus CABG group, and lowest at 26.6% in the resection group. While nearly half of the AICD and AICD plus CABG patients were seen with cardiac arrest, this was the case in the minority (6%) of the resection patients. All of the resection patients had inducible monomorphic VT on electrophysiological testing, while a number of AICD and AICD plus CABG patients had either no inducible arrhythmia or inducible polymorphic VT or VF.

Surgical Technique

The operative technique for AICD placement was largely by median sternotomy or left anterior thoracotomy. Sternotomy was used exclusively for AICD placement when an associated open heart operation was required. All patients with critical coronary artery lesions or clinical ischemia underwent associated CABG. Coronary artery bypass grafting was done with either vein or internal mammary artery conduits under cardioplegic arrest with the distal anastomoses performed first. The AICD patch placement and defibrillation testing were done after the termination of cardiopulmonary bypass, decannulation, and achievement of hemostatsis. Sternotomy also was used when no open heart procedure was necessary and the cardiac condition made it unlikely that such a procedure would be required in the future.

The thoracotomy approach was used when the patient had undergone a prior open heart operation, to eliminate the necessity for redissection of the heart. The thoracotomy approach involved placement of a superior vena cava spring electrode and a left ventricular patch electrode, or two ventricular patches. If the threshold was adequate, one or both patches were placed extrapericardially. If necessary, a patch was moved intrapericardially by local-

Table 1. Clinical Characteristics by Procedure

Variable	AICD (n = 61)	AICD + CABG (n = 28)	Directed Resection (n = 34)
Mean age (yr)	59.6	64.6	64.2
Sex (M/F)	48/13	26/2	24/10
Mean EF (%)	34.7	31.2	26.6
Cardiac arrest (%)	47.5	50	6
Electrophysiological morphology			
Noninducible (%)	16	11	0
VT (monomorphic) (%)	69	61	100
VT (polymorphic) or VF (%)	15	28	0

AICD = automatic implantable cardioverter defibrillator; CABG = coronary artery bypass grafting; EF = ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

ized dissection of adhesions. The thoracotomy approach was also preferred in certain patients in whom mild coronary or valvular disease might necessitate a later open heart operation and in certain young women for cosmetic reasons. Defibrillation testing and follow-up were done along established guidelines.

The electrophysiologically directed surgical approach in all patients was by subendocardial resection. Most patients undergoing a directed procedure had elective preoperative placement of an intraaortic balloon pump the night before operation to optimize hemodynamics and smooth the perioperative recovery. The resection was guided by epicardial and endocardial mapping using a single hand-held roving electrode during induced ventricular tachycardia. The actual resection was done under cardioplegic arrest in all but 1 patient. In the earlier part of the series, resection of the papillary muscle and consequent mitral valve replacement was performed when necessary for extirpation of a posterior arrhythmia focus. In these instances, mitral valve replacement was performed through the ventriculotomy. In the more recent part of the series, cryoablation (−60°C for two minutes) has been used as an adjunct to subendocardial resection, especially over the ventricular septum and at the papillary muscles.

When the AICD became available, most patients undergoing directed resection also had AICD patches placed at the time of the original operation to facilitate AICD placement for persistent arrhythmia or postoperative inducibility. Judicious defibrillation threshold testing was done after the termination of cardiopulmonary bypass in these patients. If major ventricular arrhythmia was inducible at postoperative testing 1 week after directed resection, the AICD was implanted. This was done even if the clinical arrhythmia had been eliminated and a nonclinical sustained VT was induced.

Follow-up

Follow-up information was obtained on the basis of return visits to our own facilities, at times supplemented by information from referring physicians as well as telephone interviews with patients.

Results

Operative Mortality

Overall operative mortality (defined as any death within 30 days of operation) was 9 (7.1%) of 127 patients. For AICD procedures, there were five deaths (5.6%) among 89 patients. Two (3.3%) of the 61 patients undergoing AICD placement alone and 3 (10.7%) of the 28 patients having AICD placement plus CABG died. For resection procedures, there were four deaths (11.8%) among 34 patients. There is no significant difference in mortality between the AICD plus CABG group (10.7%) and the resection group (11.8%). In fact, the difference in mortality between all AICD procedures (5.6%) and resection procedures (11.8%) is also not significant.

Two of the four deaths in the resection patients were due to arrhythmia, and two were due to pump failure. Of the two deaths in the straight AICD group, one occurred intraoperatively in a patient taken to the operating room with frequent runs of hypotensive ventricular tachycardia whose postmortem examination disclosed advanced cardiac amyloidosis, and one occurred as a result of a noncardiac cause (liver failure from amiodarone toxicity). Among the three deaths in the AICD plus CABG group, two were due to arrhythmia and one to pump failure.

Morbidity

The main morbidity encountered related to the AICD was late infection of the system, which was seen in 3 (3.6%) of 84 survivors. This necessitated removal of the system in all 3 patients. The system was replaced through another route in 2; in the other patient, the system was not replaced, as the patient had had CABG as well and arrhythmia was no longer inducible in the electrophysiology laboratory postoperatively.

One patient required repositioning of a migrated superior vena cava spring electrode. Two patients required psychiatric hospitalization because of anxiety related to fearful anticipation of device discharge. We have not encountered a single instance of pericardial constriction, coronary artery erosion, coronary graft erosion, or coronary graft constriction or closure, all of which have been reported as delayed complications of the AICD.

There were few complications attributed directly to endocardial resection. One patient was seen 3 years after resection with an infected false aneurysm at the site of closure of a posterior aneurysm where resection had been performed. This was successfully repaired. There were no cerebrovascular accidents in this series despite mapping of the open and beating left ventricle.

Electrophysiological Follow-up

Ten (33%) of the 30 survivors of resection had inducible VT or VF at postoperative electrophysiological study. Our electrophysiology team considered the test positive even if the rhythm induced was different from the clinical arrhythmia.

Thirty-two of the 89 AICD and AICD plus CABG patients had device discharges. Only 2 of the 10 resection patients who also had AICD patches or the AICD itself placed had discharges for ventricular arrhythmia. The first discharge occurred within the first 6 months in 32 (94%) of the 34 patients who experienced discharges during the course of the study.

In the AICD group, 51 (61%) of 84 were on a regimen of antiarrhythmic medications compared with 10 (33%) of 30 in the resection group, a significant difference at the level of p less than 0.05. These differences in susceptibility to device discharge and requirement for antiarrhythmic medications point toward a higher quality of life in the resection group.

Late Mortality

Figure 2 shows actuarial survival (freedom from all deaths). At 6 months, 86% of patients were alive in both the AICD and resection groups. Although not of significance, the curves cross at this point, with survival greater in the resection group from that point on. Survival at 2 years was 78% in the resection group and 72% in the

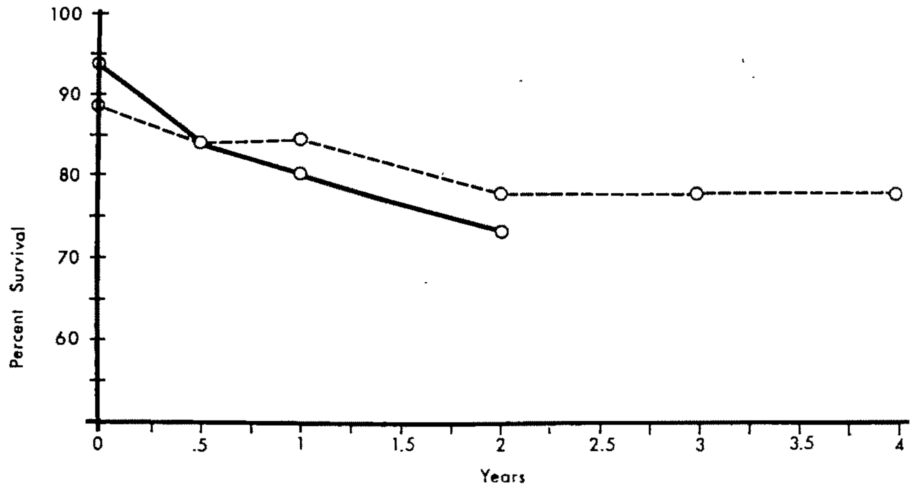

Fig 2. Actuarial survival (operative deaths included). (solid line = *placement of automatic implantable cardioverter defibrillator [AICD] ± coronary artery bypass grafting [CABG];* broken line = *directed resection ± CABG ± AICD.)*

AICD group. There were no deaths beyond this point in the resection group, so survival was also 78% at 4 years.

Figure 3 shows actuarial freedom from sudden death. Operative mortality is included. Ninety-five percent of the AICD group and 92% of the resection group were free from sudden death. At the time of follow-up, there had been no sudden deaths in the resection group after the immediate perioperative period. The curve for freedom from sudden death is completely flat up to the 4-year end point. In the AICD group, 1 patient died late because of an untoward interaction between a permanent pacemaker and the AICD. The pacemaker continued to pace during VF, thereby preventing appropriate AICD detection and discharge.

Among all patients in the study, only EF correlated with operative death. Eighteen of the 25 deaths occurred among the 68 patients with an EF less than 30%, and only 7 occurred among the 59 patients with an EF greater than 30%. Ejection fraction in the patients who died (26%) was significantly different from that in survivors (33%) ($p < 0.03$). Clinical arrhythmia (syncope, cardiac arrest, palpitations), electrophysiological findings (induced VT, induced VF, noninducible arrhythmia), and age were not predictive of mortality.

Comment

For resection procedures, our rates of operative mortality, inducibility at postoperative study, and long-term survival are similar to those collected by Cox [3] in his recent review of worldwide experience.

There is no question that the advent of the AICD has profoundly influenced the surgical strategy in the management of life-threatening, refractory ventricular arrhythmias. In general, the AICD has been found to be a low-risk and effective intervention. Surgical mortality has been in the range of 3% [6], a figure similar to that in our series. Yearly sudden death is reduced to a rate of about 2% in patients with an AICD in place [6]. This has led certain authors [5, 7–10] to advocate curtailment of directed resection, with its well-known substantial operative mortality, in favor of AICD placement with or without associated CABG depending on the patient.

Our study finds a higher surgical risk for the AICD, especially with concomitant CABG, than is suggested in previous reports. In our study, the operative mortality was 5.6% for all AICD procedures and 10.7% for those including CABG. Twenty-eight of 89 AICD procedures in our series involved CABG. Other studies [5, 7, 11] had

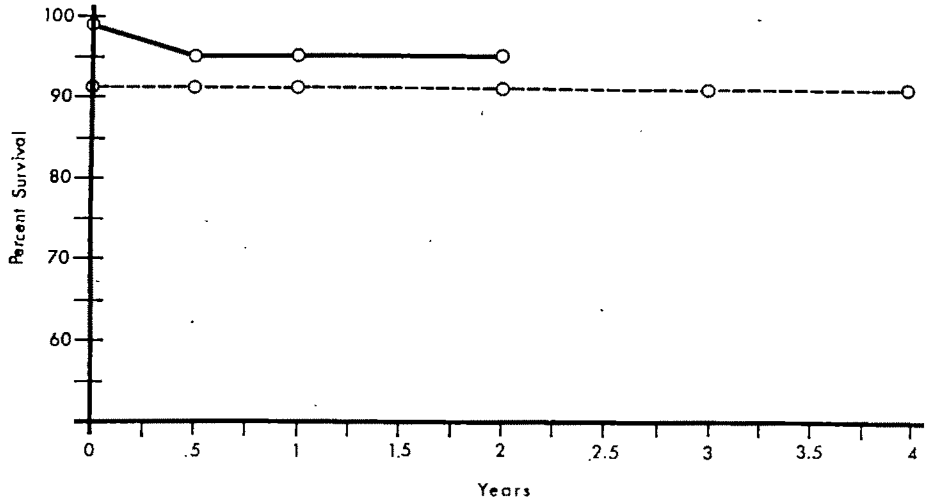

Fig 3. Actuarial freedom from sudden death (operative deaths included). (solid line = *placement of automatic implantable cardioverter defibrillator [AICD] ± coronary artery bypass grafting [CABG];* broken line = *directed resection ± CABG ± AICD.)*

smaller numbers of AICD plus CABG procedures and often did not analyze the risk of this subset separately. In one series [11], the mean EF in the group having AICD placement plus CABG was reasonably well preserved at 42%. In our series, the mean EF in the AICD plus CABG group was 31.2%. One important conclusion from our study is that even with the nonresection approach of AICD placement plus CABG, the risk of in-hospital death is substantial, reflecting the fact that the patients undergoing such procedures have severe left ventricular dysfunction from infarction and a marked propensity for life-threatening arrhythmia. Postoperative deaths were due to pump failure or arrhythmia. For all patients in our series having either procedure, EF less than 30% correlated with death at some point in the study.

A direct comparison between our AICD plus CABG and resection patient groups is not totally appropriate, as some patients in the AICD group did not represent suitable candidates for resection, for example, those without discrete aneurysm or with VF as the preoperative rhythm. This disparity in the groups might not be as severe as expected if patients without aneurysm but with discrete infarction are considered candidates for resection, as suggested by Moran [12]. It remains for future studies to compare outcome in patients who would be candidates for either procedure, AICD placement or directed resection. Ideally, these studies would look also at the functional and the symptomatic states to assess possible hemodynamic benefits of resection.

Analysis of the data from the present study leads us to believe that endocardial resection remains a very important part of the surgical armamentarium for refractory ventricular arrhythmias.

It is important to examine the relative advantages and disadvantages of the two modalities, directed resection and AICD placement. First and foremost, whereas directed resection is curative in the majority of patients, the AICD is palliative only. Resection prevents the arrhythmia, whereas AICD placement accepts that the arrhythmia will continue to occur and aims to prevent death from the arrhythmia.

The AICD imposes drawbacks in life-style that directed resection does not. The device itself is bulky and may be uncomfortable and cosmetically unsatisfactory, especially in thin patients. Discharges are uncomfortable and frightening, as is the prospect of vulnerability to sudden shocking at any instant. Frequent visits for generator checks are required (about every 3 months). Frequent replacement of the generator is required (about every 2 years). The majority of patients—61% in our study, as in other studies—require medications to decrease the frequency of ventricular ectopy. Furthermore, inappropriate discharges for atrial fibrillation or sinus tachycardia or nonsustained VT continue to be a problem.

Our study finds AICD placement not as benign as initially anticipated. Although straight AICD placement carried a hospital mortality of only 3.3%, only patients without critical coronary artery disease outside the infarct zone were selected for straight AICD placement. We took as a basic tenet that critical ischemia must be eliminated before refractory ventricular arrhythmias are accepted and palliated by AICD insertion. The importance of revascularization and the beneficial effect on malignant ventricular arrhythmias are well substantiated [13–16]. Accordingly, in our study, all patients with major coronary artery disease outside the infarct zone underwent associated CABG. The combination of CABG and AICD placement carried a mortality of 10.7%. This is not terribly surprising, as patients in this category have both severe left ventricular dysfunction from prior infarction and life-threatening ventricular arrhythmias. In these patients, CABG alone would be expected to carry increased risk. The postoperative milieu can exacerbate preexisting arrhythmias, and in 2 patients in our AICD plus CABG group, intractable arrhythmias led to postoperative death. Pump failure was the cause of another death. The low mortality rates publicized for the AICD often are unduly biased by inclusion of low-risk patients without coronary artery disease. In our study, the risk of directed resection was not significantly different from that of AICD placement with CABG.

Major morbidity was associated with AICD placement. Infection of the system, seen in 4% of patients, was a major complication. This always necessitated removal of the system and, usually, its replacement through a different approach. Hospitalization was long for patients with infection. Lead problems necessitating operative correction were seen in 1 patient. Device malfunction—an untoward interaction between a permanent pacemaker and the AICD—occurred in 1 patient and resulted in death. We saw no cases of constrictive pericarditis, coronary artery erosion, coronary graft erosion, or graft constriction or occlusion from the AICD patches.

It is important to realize that worldwide experience is too limited to anticipate fully the long-term complications of the AICD system. Constriction, erosion, and graft compromise may be seen with increasing frequency as devices remain in place. Phrenic nerve damage from the discharge current may be seen. The effects on the myocardium of repeated discharges are not fully known. Presence of the AICD patches may reasonably be expected to render subsequent CABG difficult or impossible.

None of these problems are pertinent in survivors of directed resection. In general, these patients are well and relatively free from arrhythmia and antiarrhythmic medications. Quality of life is good unless left ventricular impairment is extremely severe.

On the basis of this concurrent experience with both directed resection and AICD placement with or without CABG, we believe that both procedures are necessary elements of the contemporary surgical armamentarium for refractory ventricular arrhythmias. Resection may deliver a better return in life-style and perhaps in longevity, but possibly at a somewhat higher cost in terms of early mortality. For patients with nonischemic VT, the AICD is the intervention of choice, as directed resection is currently not applicable. If it appears likely that ischemia precipitated the arrhythmia, as with critical coronary artery disease without scar on ventriculography, we perform CABG, place patches, and test for inducibility postoperatively to determine if the AICD generator needs to

Table 2. Decision Making for Placement of Automatic Implantable Cardioverter Defibrillator Versus Directed Resection

Factor	Favor Device	Favor Resection
Frequency of arrhythmia	Infrequent	Frequent
Surgical ease and risk of resection	Severely impaired residual myocardium	Reasonably preserved residual myocardium
	No discrete aneurysm	Discrete aneurysm
	Posterior aneurysm	Anterior aneurysm
Likelihood of eliminating arrhythmia	Multiple-morphology VT	Single-morphology VT
	Polymorphic VT	Monomorphic VT
	VF	VT

VF = ventricular fibrillation; VT = ventricular tachycardia.

be implanted. Directed resection is not applicable in this setting.

The choice between AICD placement and directed resection arises for patients with ischemic VT or VF originating in scar from a prior myocardial infarction. We recommend individualized decisions based on the assessment of three factors in each particular patient: (1) the frequency of the arrhythmia, (2) the anticipated ease and operative risk of directed resection, and (3) the likelihood of eliminating the arrhythmia by directed resection. Table 2 schematizes the factors we use in these assessments.

There is a wide range in the frequency with which patients manifest their ventricular arrhythmias. Some have only a single event. Others have events many times a day. One of our most emergent directed resections was performed in a surgeon with recalcitrant arrhythmia 12 years after an anterior infarction. He sustained VT more than 100 times during one weekend and required the cardiologist at the bedside almost constantly for overdrive pacing or direct-current cardioversion. This patient has returned to his practice, needs no medications, and has no arrhythmias whatsoever after directed resection. This case represents one extreme of frequency for which elimination of the arrhythmia represents a much better solution than its acceptance and conversion on an as-needed basis by the AICD. In general, if a patient manifests the arrhythmia more than once or twice a month, despite administration of antiarrhythmic medications, we are inclined more toward directed resection.

The literature [3] supports the fact that ventricular function is the most important factor in determining surgical risk for directed resection. In particular, we emphasize the level of function in the remaining viable muscle outside the infarct zone in which the arrhythmia originates. Our decision making is based more on the overall subjective appearance of the left ventriculogram than on the calculated EF. If the muscle outside the infarct zone to be approached moves adequately, we are more inclined to proceed. If multiple remote areas are infarcted or overall contractility is impaired, we are inclined to avoid resection. We also factor ease of resection into this decision making. Discrete aneurysms are easier to work through than infarcts without aneurysm. Anterior aneurysms provide better exposure for resection with less danger to the mitral apparatus than inferior ones, although we routinely approach inferior aneurysms and have had good results.

Multiple factors enter into our assessment of the likelihood of extirpating an arrhythmogenic focus by a directed procedure. If the rhythm is VF rather than VT, it cannot be mapped, so the likelihood of extirpation is expected to be less. A single site of monomorphic VT is the most promising for directed resection. Multiple morphologies of monomorphic VT or polymorphic VT are less promising.

We have the impression that prophylactic preoperative placement of an intraaortic balloon pump in most of our patients having directed resection has been of benefit. In general, weaning from bypass has not been a problem. Most patients have done well without inotropic medications. The avoidance of these medications and the maintenance of good hemodynamics are probably of benefit in avoiding early postoperative arrhythmias in patients undergoing directed resection.

Our review of our concurrent experience with AICD placement and directed resection demonstrates the following:

1. Ejection fraction less than 30% correlated with death in the overall population treated by both surgical means.
2. Operative mortality for AICD plus CABG was substantially higher than previously appreciated (10.7%). Further confirmation is required as experience grows.
3. Implantation of an AICD (in many instances with CABG) and directed resection had similar operative mortality rates (not significantly different).
4. Patients undergoing directed resection were less likely to require antiarrhythmic medication.
5. Overall survival and freedom from arrhythmia-related death were excellent with both modalities.

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DISCUSSION

DR IRVING L. KRON (Charlottesville, VA): I congratulate Elefteriades and associates on an excellent presentation and a carefully studied group of patients. Their mortalities for endocardial resection and AICD implantation were very acceptable. However, 33% of patients with endocardial resection had a positive postoperative electrophysiological study and therefore received drug therapy.

Elefteriades and associates were very rigorous in determining whether or not the operation worked and counted any sustained VT at postoperative study as a failure. I congratulate them for this and believe this should be the standard for VT surgical reporting. Most surgical series would count a so-called nonclinical VT at postoperative studies as unimportant.

These nonclinical arrhythmias are real and should be treated as such. Miller and co-workers [Miller JM, Kienzle MG, Harken AH, Josephson ME. Morphologically distinct sustained ventricular tachycardias in coronary artery disease: significance and surgical results. J Am Coll Cardiol 1984;4:1073–9] noted that some nonclinical arrhythmias actually recurred spontaneously postoperatively. The mechanism for different arrhythmias induced postoperatively may be different morphologies or alteration by the surgical procedure.

As Elefteriades and associates suggest, there has been an evolution away from endocardial resection in favor of AICD implantation. That is why it is critical that the results of endocardial resection must be improved.

My colleagues and I differ mostly from Elefteriades and associates in the technique of operation. We feel strongly that the resection should be performed on the beating heart and mapping and resection continued until no further VT can be induced. Before this change in technique our postoperative inducibility was 27%; it is now down to 12%. Dr Elefteriades, why do you perform resection under cardioplegic arrest?

Placement of an AICD usually requires concomitant drug therapy, which is not benign. All of the drugs carry substantial potential for adverse effects [Nygaard TW, Sellers TD, Cook TS, DiMarco JP. Adverse reactions to antiarrhythmic drugs during therapy for ventricular arrhythmias. JAMA 1986;256:55–7].

Dr Elefteriades, why is the proportion of AICD placement so high? My main concern is that endocardial resection will be reserved for the high-risk patients, such as those in shock; such patients represented 4 of 6 deaths in our series. I believe both methods have a role. As you pointed out, combined CABG and AICD had a mortality similar to that of endocardial resection. If the arrhythmia was mappable, would you consider endocardial resection when merely an infarct was present without an aneurysm?

DR ELEFTERIADES: The proportion of AICD placement was high, and this reflects two factors. One is that 19 of the patients were not coronary patients at all. Some of them were young patients with healthy hearts and arrhythmia. The high proportion of AICD placement also represents the preference of part of our electrophysiology team, and this is one of the reasons that we presented data, to modify the prejudice that some electrophysiologists have against resection.

Regarding the technique of operation, we agree entirely with what Dr Kron has said, and we are beginning to gain experience with the technique that he has described of doing the resection in a beating heart. This is probably the procedure of choice. Indeed, it is a wonderful feeling to have the patient in sustained VT when you cut the arrhythmia focus. It gives you an absolute confirmation that you have gotten the arrhythmia out.

On the question of whether to resect if the patient is mappable and has no aneurysm, we would again agree entirely with Dr Kron that it is very reasonable to approach such an arrhythmia focus through the infarct.

Improved Patient Survival After Cardiac Arrest Using a Cardiopulmonary Support System

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A portable cardiopulmonary bypass system that can be rapidly deployed in a nonsurgical setting using nursing staff was used in 38 patients with cardiovascular collapse refractory to ACLS protocol. Percutaneous or cutdown cannulation sites were: femoral vein–femoral artery (n = 18), right internal jugular vein–femoral artery (n = 2), right atrium–ascending aorta (n = 12), or a combination approach (n = 4). Two patients could not be cannulated. Patient diagnoses were pulmonary emboli (n = 3), failed coronary angioplasty (n = 7), myocardial infarction with cardiogenic shock (n = 5), trauma (n = 7), aortic stenosis (n = 2), postcardiotomy deterioration (n = 10), deterioration after cardiac transplantation (n = 2), cardiomyopathy with shock (n = 1), and ruptured ascending aortic dissection (n = 1). Ninety-five percent of patients (36 of 38) were successfully resuscitated to a stable rhythm. Eight diagnostic procedures (coronary angiography, n = 4; pulmonary angiography, n = 3; and aortography, n = 1) were performed while patients were on cardiopulmonary support. Early deaths resulted from massive hemorrhage (n = 8), inability to cannulate (n = 2), and irreversible myocardial injury (n = 10). Sixty-six percent (24 of 36) of patients successfully cannulated underwent conversion to standard cardiopulmonary bypass with attendant operative procedure or placement of ventricular assist device or total artificial heart. Fifty percent (18 of 36) of patients cannulated were successfully weaned from cardiopulmonary support, and 17% (6/36) are long-term survivors. Postweaning deaths resulted from central nervous system failure (n = 5), multisystem failure (n = 3), anemia (n = 1, Jehovah's Witness), peripheral pulmonary emboli (n = 1), support withdrawn (n = 1), and sudden death due to arrhythmia (n = 1). Cardiopulmonary support has salvaged 6 patients in our series of 38 who were not able to be resuscitated by conventional techniques. The cardiopulmonary support system supports patients who have experienced sudden death and allows diagnostic and therapeutic interventions to be applied. Survival is coupled to early implementation and reversibility of the conditions that led to patient death. Cardiopulmonary support is ineffective in late cardiogenic shock resulting from massive myocardial infarction or in trauma patients with uncontrolled hemorrhage.

(Ann Thorac Surg 1990;49:101–5)

Cardiac arrest and sudden cardiac death account for approximately 300,000 deaths annually in the United States, nearly 50% of all cardiovascular deaths [1]. Techniques of closed chest massage for cardiopulmonary resuscitation (CPR) were popularized by Dr William Kouwenhoven and associates of Johns Hopkins in 1960 [2]. Since then, different methods of circulatory assistance [3, 4] have been applied to CPR techniques in an effort to improve survival. Results of CPR are a function of the mechanism of arrest, location of arrest, and underlying pathology. In 1983, Bedell and colleagues [5] reported that only 14% of patients who survived in-hospital cardiac arrest were successfully discharged. Increased understanding of extracorporeal circulation and perfusion techniques lends itself to application in the setting of cardiac arrest that is believed to be reversible with or without operative management.

Material and Methods

Cardiopulmonary Support System

The cardiopulmonary support (CPS) system used in all cases is manufactured by C.R. Bard. The CPS mobile cart houses a Bio-Medicus centrifugal pump controller, a 28-V battery source along with charger, a Normotherm heater, and an E cylinder (oxygen). The disposable software includes thin-walled 20F Teflon venous and arterial cannulas with sideholes, a Bio-Medicus centrifugal pump head, a Scimed heat exchanger, and a hollow-fiber oxygenator, all prepackaged with connecting tubing. Stored along with the hardware and software package are sterile instrument trays for vascular cutdown procedures and a chest tray with a USCI 1969 venous cannula and Sarns 6.5-mm high-flow aortic cannulas. With this equipment, cannulation sites may be individualized, with venous drainage through the right or left femoral veins, right internal jugular vein, right atrium, or combinations of these. Ideally, the tip of the venous cannula should be in the right atrium. Similarly, arterial return may be accomplished through the right or left femoral artery or the ascending aorta. Peripheral cannulation may be performed by surgical exposure of the surface of the access

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Table 1. Patient Characteristics[a]

Sex	Age (yr) Range	Age (yr) Mean
F	12–83	51
M	8–78	56

[a] Patients in whom cardiopulmonary support was attempted between June 1986 and August 1988.

Table 2. Patients Transferred to Operating Room

Procedure	n	Early Survivors	Late Survivors
Control of hemorrhage	9	6	3
Coronary artery bypass grafting	7	5	3
Pulmonary embolectomy	3	2	0
Repair of aorta	3	2	0
Placement of left ventricular assist device	1	1	0
Placement of Jarvik-7	1	1	0
Total	24	17	6

vessels or by percutaneous puncture using modified Seldinger technique [6, 7].

The cart and instrument packs are stored in the intensive care unit. If the device is required elsewhere in the hospital, it is transported by a trained intensive care unit nurse who is responsible for priming and conduct of CPS. Placement of cannulas is performed by cardiovascular surgeons, trauma surgeons, or cardiologists. A perfusionist takes out-of-hospital call responsibility and is readily available.

Flows of up to 6 L/min have been obtained with satisfactorily placed cannulas. Diagnostic studies such as pulmonary angiography, coronary angiography, or aortography can be performed without difficulty while the patient is on CPS. Definitive operative procedures such as pulmonary embolectomy, coronary artery bypass grafting, major arterial repair, or placement of assist devices (left ventricular, right ventricular, biventricular, or total artificial heart) are easily performed. If conversion to standard cardiopulmonary bypass (CPB) is chosen, a Hemocron filter is used to lessen the problems of fluid overload and excess hemodilution.

Patients

From June 1986, to August 1988, CPS was used in 38 patients with cardiac arrest at Sharp Memorial Hospital, University of California at San Diego Medical Center, or Palomar Memorial Hospital. Each of these 38 patients had sudden catastrophic loss of their cardiac rhythm and hemodynamics and could not be resuscitated by ACLS protocol [4].

Of the 38 patients in the series, 13 (34%) were female and 25 (66%) were male. Ages ranged from 8 to 83 years (mean, 57 years) (Table 1). Among the 38 patients, 10 (26%) had postcardiotomy deterioration, 7 (18%) had failed coronary angioplasty, 7 (18%) had major trauma, 5 (14%) had myocardial infarction with cardiogenic shock, 3 (8%) had massive pulmonary embolus, 2 (5%) had aortic stenosis, 2 (5%) had deterioration after cardiac transplantation, 1 (3%) had cardiomyopathy with shock, and 1 (3%) had a ruptured acute dissection of the ascending aorta.

Cannulation approach was individualized. Twelve patients (32%) in whom a recent sternotomy or lateral thoracotomy was accessible were cannulated through the right atrium and ascending aorta directly. Femoral vein and femoral artery cannulation were used in 18 patients (47%). The right internal jugular vein and femoral artery were used in 2 patients (5%). A combination of approaches was used in 6 patients (16%).

Eight diagnostic procedures were performed while patients were on CPS. Four patients had coronary angiograms, 3 had pulmonary angiograms, and 1 had aortography.

Results

Of 38 patients in whom CPS was attempted, 36 (95%) were successfully resuscitated to a stable rhythm. The remaining 2 patients represent our early experience in which cannulation through the femoral vein was unsuccessful and no further attempts were made at venous access.

Eighteen of the 36 patients in whom CPS was successfully placed were successfully weaned. Of those who could not be weaned, 8 had massive uncontrollable hemorrhage and 10 had massive myocardial infarction.

Twenty-four patients were taken to the operating room, 9 for control of hemorrhage, 7 for coronary artery bypass grafting, 3 for pulmonary embolectomy, 3 for repair of the aorta, 1 for placement of a left ventricular assist device, and 1 for explanation of a transplant graft and implantation of a Jarvik-7 artificial heart. Sixteen of these 24 patients were transferred to standard CPB (Tables 2, 3).

Twelve patients who were weaned from CPS died later in their hospital course: 5 died of central nervous system failure, 3 of multisystem failure, 1 of anemia, and 1 of peripheral pulmonary emboli not surgically accessible; in 1 patient support was withdrawn, and there was one sudden death. One of the central nervous system failures resulted from anoxic insult in which oxygen was not delivered to the perfusion circuit. The patient with severe

Table 3. Results in 36 Surviving Patients Who Received Cardiopulmonary Support (n = 36)

Result	n (%)
Stable hemodynamics	34 (94)
Taken to operating room	24 (67)
Converted to full CPB	16 (44)
Early survivors (weaned from CPS)	18 (50)[a]
Late survivors	6 (17)

[a] One Jarvik-7, one left ventricular assist device, one biventricular assist device.

CPB = cardiopulmonary bypass; CPS = cardiopulmonary support.

anemia refused blood transfusion on the basis of religious beliefs. The patient from whom support was withdrawn had a ruptured coronary artery after angioplasty. This patient and her family declined operative intervention. She died 60 minutes later.

Six patients survived long term and were discharged from the hospital. Three of these patients underwent coronary artery bypass grafting after failed angioplasty. One of these patients had previously undergone coronary artery bypass grafting. Sternotomy in this patient while on CPS was greatly facilitated in that the heart was decompressed and all adhesions were stretched. The other 3 patients who survived long term were resuscitated from massive hemorrhage after cardiotomy.

Comment

Modifications of CPR techniques have evolved based on anecdotal data and have come under scrutiny by the scientific community [8]. Closed cardiac massage can provide only 10% of normal cerebral blood flow and only 5% of myocardial blood flow [8]. Use of open chest cardiac massage may well provide better blood flow to these critical areas. Decades have passed since the inception of CPR, but in-hospital resuscitation still has a poor prognosis, with only 14% of resuscitated patients living long enough to leave the hospital [5].

An external power source to provide CPS has long been desired. The concept of extracorporeal CPS support was set forth by LeGallois in 1813 [9], although it did not become a clinical reality until 1953 as performed by Gibbon [10]. The initial impetus to develop CPB was to provide adequate systemic circulation in patients with a massive pulmonary embolus. The simple pump-oxygenator rapidly grew into massive electronic consoles requiring four roller-pump heads [11, 12]. This, coupled with unacceptable embolic rates and disruption of formed blood elements, slowed clinical progress [13]. Configurations of venovenous and venoarterial bypass were evaluated. Goldman and colleagues [14] showed the superiority of venoarterial pumping in ventricular fibrillation. Because access to the venous reservoir provided improved preload to the system, higher flows were obtained. Use of membrane oxygenators lessened the problem of disruption of the formed blood elements with prolonged perfusion [15]. Techniques of percutaneous femoral cannulation [16, 17] along with improved understanding of extracorporeal perfusion methods ushered in the concept of a portable CPS system to be used in the hospital.

We used CPS in patients in whom standard CPR was ineffective and in whom a fatal arrhythmia was believed to be reversible. We also used it in cardiac arrest patients in whom the diagnosis was unclear. In such patients, CPS provided time to perform diagnostic studies. When aortography is performed, the CPS must be slowed and the heart allowed to eject. Similarly, pulmonary angiography requires that the contrast medium be injected distal to the pulmonary valve with the right heart ejecting. Because of the additional data obtained from these studies, patients with no reversible pathology were spared an unnecessary thoracic procedure.

Mattox and Beall [9] reported 39 patients in a moribund state who were placed on a portable CPB: 15 were long-term survivors; 13 of them had had massive pulmonary embolus. Phillips and colleagues reported 21 patients with refractory cardiac arrest. Seventeen patients could be resuscitated; 4 trauma patients could not [Phillips SJ, personal communication].

The clinical effectiveness of CPS is difficult to evaluate. Use of CPS improves tissue perfusion, as evidenced by correction of acidosis and ability to cardiovert the heart to a regular rhythm. We estimate that mortality would be 100% in our group of patients if they had not been treated. Sixteen percent of our treated patients survived. These results closely paralleled the early results of a 1973 study [18] using intraaortic balloon counterpulsation to treat cardiogenic shock: of 87 patients, there were 35 early survivors but only 15 survivors left the hospital.

It is natural for physicians to be hesitant to apply any new mechanical support devices with unproven track records in only the most desperate situations in hopelessly ill patients. We trust that these results will not delay use of this technology in select patients.

Conclusion

Our early experience in these patients was punctuated with difficulty in cannulation as well as a high proportion of central nervous system dysfunction. Design changes have remedied the former problem. Late institution of CPS coupled with ineffective CPR have prompted us to initiate CPS earlier and may produce less central nervous system dysfunction. Use of CPS in trauma patients has been disappointing in our series as well as those of other investigators [17, Phillips SJ, personal communication]. Heparinization tends to worsen the grave situation. With the advent of heparinless oxygenators around the corner, careful evaluation of CPS in these patients is warranted.

We had limited success using CPS in patients with acute myocardial infarction before onset of cardiogenic shock. Resuscitation of the postcardiotomy patient who exsanguinates is performed easily with CPS. Cardiopulmonary support may be used in hypothermic patients or those with cardiodepressant drug toxicity. Although mortality may not decrease with more widespread use of CPS in cardiac arrest, we recommend a careful clinical trial involving earlier implementation in select critically ill patients.

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DISCUSSION

DR WALTER E. PAE, JR (Hershey, PA): I congratulate Dr Reichman and the group at Sharp Memorial for their fine presentation and thank them for the privilege of reviewing their manuscript before this presentation.

At The Pennsylvania State University Hospital in conjunction with our colleagues at the Harrisburg Hospital, using this same CPS system during the last 3 years, we initiated bypass outside the operating room in 15 patients after failure of standard advanced life support measures. The patients' diagnoses were quite similar to those of the patients of Dr Reichman and colleagues.

All 15 patients were stabilized hemodynamically, with mean bypass flows of approximately 4L/min; they had average bypass times of 110 minutes. Similar to the experience of Reichman and associates, 7 of our 15 patients, or about 50%, were ultimately weaned. Only 2 of the 7 patients had cardiac and neurological recovery, however. Nonetheless, there were no survivors when the system was used in patients receiving cardiopulmonary resuscitation longer than 30 or 40 minutes before bypass or in patients who had an unwitnessed cardiac arrest.

In our experience, cannulation and therefore rapidity of deployment has been most optimal in the cardiac catheterization laboratory, using a modified Seldinger technique such as Reichman and associates described, in which the femoral vessels were surgically visualized—before puncture and fluoroscopy was available. Cannulation is also easily achieved in the intensive care unit, where the chest of a postoperative cardiac patient can be rapidly reopened and direct cannulation can be achieved. Our early experience using a true Seldinger technique, although successful in achieving cannulation, was more cumbersome and time-consuming in patients without palpable pulses and resulted in some complex vascular injuries.

This technology does represent a powerful adjunctive therapy in properly selected patients to allow subsequent diagnostic and therapeutic maneuvers, but unless the uncovered pathology is correctable and the intervention itself does not lead to significant morbidity, meaningful recovery will probably not occur.

I would like to direct several questions to Dr Reichman. First, in terms of patient selection, do you believe that this technology has any application in the treatment of an unwitnessed cardiac arrest or have you placed a time limit on pre-bypass CPR as a patient selection criterion?

Second, in deference to our cardiology colleagues and despite improvements in cannula design, do you believe that direct visualization of the peripheral vessels is important to limit complex vascular injuries and cannula malposition, and to increase the chances of a rapid successful cannulation?

Last, do you foresee an expanded role or have unreported experience in use of this particular technology as an adjunct to complex angioplasty or valvoplasty procedures in carefully, mutually selected high-risk patients?

DR WILLIAM B. IAMS (Camp Hill, PA): I am concerned that this technology might be expanded to noncardiac surgeons and be run by nonperfusionists. I know that there is a commercial impetus to do this, but my particular concern is that the patient will be killed by the machine rather than saved. As shown by this series and our series, the salvage rate is small even when CPS is performed by cardiac surgeons and perfusionists. What if the CPS system is placed by less than experienced people and is run by less than experienced perfusionists? It is CPB, and I believe that this issue of credentials will arise in your own hospitals. How many survivors were cannulated from the right atrium to ascending aorta? I believe that 12 of your patients were treated in this way. Could conventional CPB not be instituted in these cases?

This technology has expanded with the great interest in providing femorofemoral bypass with excellent cannulas. These cannulas, in my experience, have been very helpful in redo coronary artery bypass patients: I can place a small catheter in the femoral artery and a small catheter in the femoral vein and, if I need to, I can cannulate percutaneously with these cannulas in a matter of minutes if a redo is decompensating and I cannot get the heart free of adhesions.

Finally, I believe that this technology is best used in the deteriorating patient but that it should not be instituted in the obviously dead patient.

DR HOOSHANG BOLOOKI (Miami, FL): I congratulate Dr Reichman and his associates for a great deal of work. This procedure requires a lot of manpower, but, as you note, provides little reward.

So long as CPS equipment is used in the cardiac catheterization laboratory for complications of angioplasty and possibly prophylactically for some of the difficult angioplasties or for left main disease, I believe it will be a helpful system. But when the indication for its use is expanded, I think we will have trouble.

At the University of Miami between 1968 and 1971, we used a very simple protocol. We thought that a patient who was doing well a few minutes before cardiac arrest would respond to resuscitation if we could reestablish cardiac output with a pump oxygenator. We had a portable heart-lung machine in the emergency room and used it in select young patients with out-of-hospital cardiac arrest if cardiac massage was not effective within ten to 15 minutes. We placed the patient on the heart-lung machine—femorofemoral bypass with oxygenation—and simultaneously opened the left chest to perform open cardiac massage. This we believed mandatory because we discovered that as soon as we stopped the external cardiac massage, the arrested heart dilated, and pulmonary edema, hemorrhage, and hypoxia followed.

The protocol called for taking the patient to the operating room, discontinuing cardiac support gradually, and closing the chest. We were also seeking an acute coronary obstruction that we could fix or bypass. We performed such procedures as on-table coronary angiography. Some of the results on this work were previously reported [Circulation 1971;44:1034–42]. We initially used the portable heart-lung machine in 7 patients. All had had out-of-hospital cardiac arrests. We had 1 survivor; this provided the impetus for us to use the device more often. Unfortunately, in the next year we used it in 7 other patients with in-hospital cardiac arrest. We expanded the indication to patients with suspected pulmonary emboli and patients with myocardial infarction and cardiac arrest, but we had no other survivors despite a great deal of effort.

Our final conclusion was that we must use some type of case stratification. Which patient would get the best result? With the small number of survivors so far, we cannot draw any conclusions. We can, however, identify patients who do not respond to this support system. We discovered that patients in the coronary care unit with cardiac arrest after cardiogenic shock were the worst candidates for this method of support. Our 1 patient who eventually did well had no coronary artery disease and had ventricular fibrillation due to cardiomyopathy that had not responded to ten minutes of cardiac massage.

Dr Reichman, can you indicate which patient group benefited most from this support system? You had 6 survivors, 3 with postoperative hemorrhage leading to cardiac arrest and 3 with cardiac arrest after coronary bypass. These would be surgical patients in the intensive care unit. Are you thinking of limiting your effort to this group of patients instead of using this device in all patients with cardiac arrest in the hospital setting?

DR HENDRICK B. BARNER (St Louis, MO): The abstract indicates that nursing personnel were used to initiate CPS. Dr Reichman, could you speak to the issue of using nursing personnel versus perfusionists for managing the CPS system?

DR REICHMAN: Dr Pae, out initial impression, although we do not have hard data to substantiate this, is that prolonged CPR and unwitnessed arrest are poor predictors of outcome. In our patients, all cardiac arrests were in-hospital arrests. No patient in our series arrived at the emergency room in an arrested state. Furthermore, if restoration of a rhythm was made possible by CPR, use of CPS to stabilize hemodynamics met with better results.

We have placed cannulas through percutaneous puncture of the right internal jugular vein, femoral vein, and femoral artery in select cases. I must caution you about this approach. One of our patients had percutaneous femoral cannulation. This patient's groin was so thick that some of the sideholes in the arterial cannulas were extravascular. This created a lethal situation. Removal of the arterial cannulas is a procedure requiring direct suture repair. We have removed jugular venous cannulas without cutdown.

As for use of the procedure in the catheterization laboratory, we have used CPS in 6 patients for elective angioplasty or valvoplasty who were considered nonsurgical candidates. These data are not included in our current report. Three of the patients had valvoplasty, 2 had coronary angioplasty, and 1 patient had combined valvoplasty and angioplasty. We performed cutdown of the femoral vessels on the right side of CPS insertion and cutdown of the left femoral artery for placement of the angioplasty or valvoplasty catheter. In an effort to decrease myocardial oxygen consumption, we cooled each patient's temperature to 34°C. At the conclusion of the procedure, each vessel was repaired primarily. Each of these catheterization laboratory patients involved a team effort. The cardiac surgeon provided vascular access, conduct of CPB was maintained by the cardiac surgeon and perfusionist, and only the formal balloon procedure was performed by the cardiologist.

Dr Bolooki, we have our unit stationed in the intensive care unit on a battery charger. Sterile vascular cutdown and reentry sternotomy trays are stored with the unit. If it is summoned to a location outside the intensive care unit, such as the medical ward or the emergency room, an intensive care unit nurse responds with the unit. Set-up and priming of the unit is her responsibility. Cannulation is performed by the surgeon; we have had trauma surgeons, cardiac surgeons, and cardiologists place the unit. Further management is performed by an on-call perfusionist who is summoned from home. The machine can be placed initially by a trained noncardiac surgeon, and initial conduct of the machine can be performed by an intensive care unit nurse with a perfusionist on call. It is inefficient to have perfusionists in house in each of these three hospitals on a 24-hour basis.

Dr Iams, of our 6 long-term survivors, 3 were cannulated through the chest, 2 through the femoral artery and vein, and 1 through internal jugular vein and femoral artery.

Successful Coronary Artery Bypass Grafting for High-Risk Left Main Coronary Artery Atherosclerosis After Cardiac Transplantation

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Severe stenosis of the left main coronary artery developed in a 58-year-old woman 9 years after orthotopic heart transplantation. Because of serious reversible myocardial ischemia and the high-risk nature of the coronary disease, coronary artery bypass grafting was performed, with no complications. Possible risk factors for the development of coronary arterial disease and its management in the transplant population are discussed.

(Ann Thorac Surg 1990;49:106–10)

Accelerated graft atherosclerosis is a major obstacle in long-term management of cardiac transplant recipients. It may be acute, occurring as sudden death, silent myocardial infarction, or acute congestive heart failure, or it may be identified as silent myocardial ischemia, detected by routine stress testing, or detected as asymptomatic coronary arterial narrowing on routine annual coronary angiography [1–3]. Attempts to identify patients who are at risk for premature coronary atherosclerosis have not had reliable results, and antiplatelet regimens and changes in the immunosuppressive therapy have not been of proven benefit. Coronary revascularization by coronary artery bypass grafting has not been advocated or attempted because of the diffuse nature of the coronary arterial disease in this population, and because chronic steroid and immunosuppressive therapy increase the risk of perioperative infections and delay in the wound healing process. Recently, successful percutaneous coronary angioplasty for discrete proximal coronary stenoses has been reported in selected patients [4].

Our patient, who underwent cardiac transplantation more than 9 years ago, had new asymptomatic proximal atherosclerotic coronary arterial narrowings 1 year before dyspnea on exertion developed; she was diagnosed as having new and severe left main arterial stenosis. Coronary revascularization was believed necessary because of the high-risk location of the coronary stenoses, evidence of serious reversible ischemia on exercise thallium scintigraphy, and the risk associated with the waiting period for retransplantation.

The patient is a 58-year-old woman who underwent orthotopic cardiac transplantation for idiopathic cardiomyopathy on December 3, 1979. Her clinical course, events, and yearly laboratory data are summarized in Table 1. She had adult-onset diabetes and required an oral hypoglycemic agent for the 3 years before her current admission to the hospital. Systemic hypertension developed 2 years before this admission and was well controlled with antihypertensive therapy. Accelerated graft atherosclerosis was first documented 6 years after transplantation, with minimal coronary arterial stenosis of the proximal left anterior descending artery and pruning of the distal vessels.

One year before her current admission, she was noted to have a 50% stenosis at the takeoff of the circumflex artery and a long 45% narrowing of the proximal left anterior descending artery as measured by digital calipers (Fig 1). The right coronary artery was free of notable disease. The myocardial blush was poor on left coronary angiography, and there was pruning of the distal vessels. Exercise thallium scintigraphy did not show evidence of reversible myocardial ischemia, although perfusion of the anterolateral wall was less than normal (Fig 2). Twenty-four-hour ambulatory monitoring of the ST segment for silent ischemia was also normal.

Seven years after transplantation, 2 years before the present admission, for unrelated reasons, her immunosuppressive regimen was changed from one of prednisone and azathioprine to cyclosporine, azothioprine, and a lowered dose of prednisone. In the 3 months before the present admission, the patient noted the onset of exertional chest discomfort and dyspnea. She was able to exercise for 8.4 minutes on a modified Bruce protocol, and thallium scintigraphy showed a large area of reversible ischemia in the anterolateral wall (Fig 3). Significant ST segment depression was evident, which was also new. Coronary angiography revealed a new 85% stenosis of the left main coronary artery, as well as progression of the disease in the proximal circumflex and left anterior descending coronary arteries (Fig 4). The hemodynamic data are shown in Table 2.

On examination, the patient appeared cushingoid, her blood pressure was 118/78 mm Hg, and cardiac examination revealed a fourth heart sound. Examination of the extremities revealed healed superficial ulcers and brawny discoloration in the lower legs. There were no obvious usable venous conduits in either the greater or lesser saphenous venous systems because of previous bilateral greater saphenous vein strippings.

The decision to perform coronary artery bypass grafting

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Table 1. Lipid Levels and Immunosuppressive and Medical Therapy During Follow-up

		Years After Transplantation								
Variable	Preoperative	1	2	3	4	5	6	7	8	9
Heart rate (bpm)	85	100	98	100	103	NA	100	112	98	100
Systolic BP (mm Hg)	100	100	125	122	118	NA	128	128	160	118
Diastolic BP (mm Hg)	70	60	70	95	78	NA	98	98	100	78
Total cholesterol (mg/dL)	NA	NA	NA	252	222	277	277	214	222	184
LDL cholesterol (mg/dL)	NA	NA	NA	109	118	188	187	120	NA	200
HDL cholesterol (mg/dL)	NA	NA	NA	38	35	35	36	26	NA	NA
Triglycerides (mg/dL)	NA	215	361	231	345	271	404	340	272	369
ASA use	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Prednisone (mg/day)	NA	20	25	25	20	20	17.5	7.5	7.5	7.5
Cyclosporine (mg/day)	NA	NA	NA	NA	NA	NA	NA	300	300	260
Azothioprine (mg/day)	NA	75	100	100	100	100	100	100	100	100
Exercise time (min)	1.0	6.5	NP	NP	6.0	NP	6.5	NP	NA	8.4
MUGA EF (%)	6	55	46	42	54	33	31	31	42	40
No. of acute rejections	NA	3	1	0	0	0	0	0	0	0

ASA = acetylsalicylic acid; BP = blood pressure; EF = ejection fraction; LDL = low-density lipoprotein; HDL = high-density lipoprotein; MUGA = multigated acquisition; NA = not applicable or not available; NP = not performed.

was made because of the patient's symptoms, evidence of serious exercise-induced ischemia, a marked myocardial perfusion abnormality, her high-risk coronary anatomy, and our belief that she was not a good candidate for retransplantation. The coronary artery bypass procedure was performed with standard techniques. A segment of vein was harvested from the right arm, and the left internal mammary artery was dissected off the chest wall. The left ventricle and apical portion of the right ventricle were encased in a markedly thickened and tightly adher-

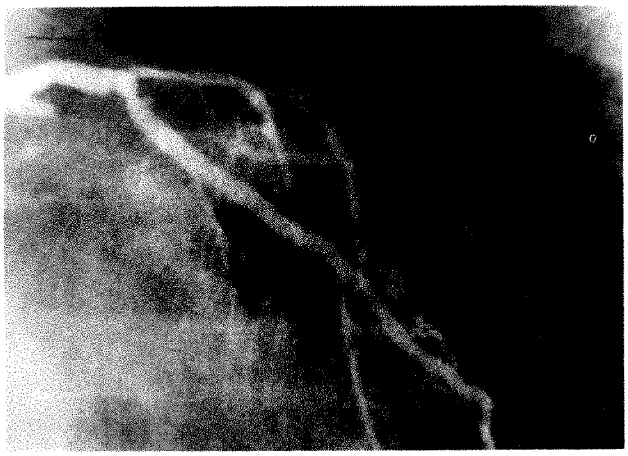

Fig 1. Left coronary angiogram in a right anterior oblique projection shows 45% narrowing of the proximal left anterior descending artery and a 50% stenosis of the proximal circumflex artery at its origin. The left main artery is free of disease.

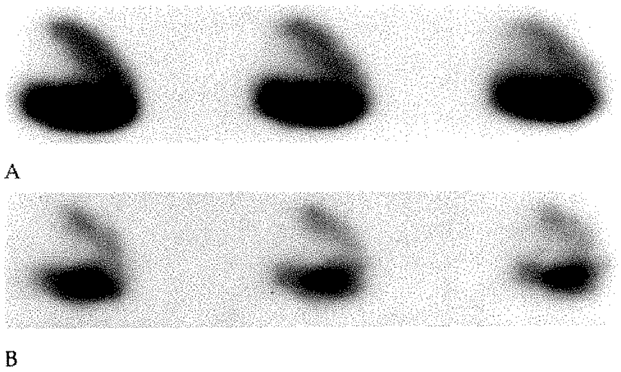

Fig 2. Exercise (A) and redistribution (B) tomographic thallium images 1 year before operation. An area of poor perfusion is apparent along the anterior wall, but no reversible ischemia was evident during the 4-hour or 24-hour resting studies. No electrocardiographic evidence of ischemia was noted.

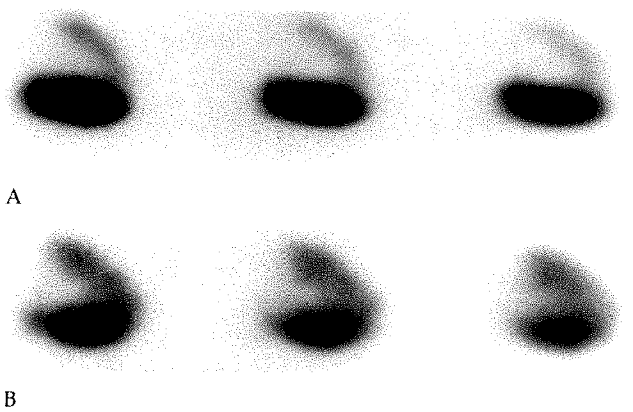

Fig 3. Exercise (A) and redistribution (B) tomographic thallium images 1 week before operation. A larger area of poor perfusion is now apparent along the anterolateral wall, which redistributes at 4 hours. New significant electrocardiographic evidence of ischemia was also noted during exercise.

ent visceral pericardium. Pericardiectomy appeared to enhance myocardial filling and contractility. Because of the relatively large size of the circumflex vessel (2 mm) and small caliber of the distal left anterior descending artery (1 to 1.5 mm) by probe calibration, we elected to anastomose the left internal mammary artery to the circumflex-marginal artery; we anastomosed the vein harvested from the right forearm to the left anterior descending artery. The patient was weaned from cardiopulmonary bypass without difficulty and was discharged on the eleventh postoperative day. An exercise thallium study performed 3 weeks postoperatively showed no evidence of reversible ischemia (Fig 5). The patient was able to exercise for 7.2 minutes despite the presence of an upper respiratory infection; she stopped because of leg fatigue, but attained a heart rate of 150 beats per minute and a systolic blood pressure of 144 mm Hg for a double product of 21,600. After 6 months of follow-up, she remains asymptomatic.

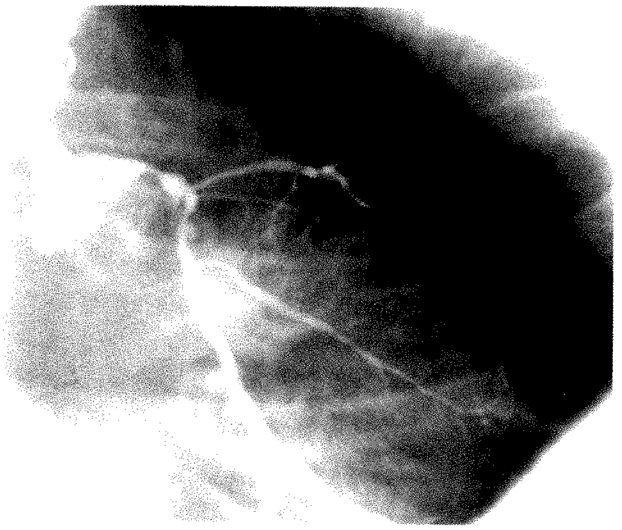

Fig 4. Left coronary angiogram in a right anterior oblique projection. The left main artery now has an 85% stenosis in its midportion.

Table 2. Hemodynamic Measurements Before Coronary Artery Bypass Grafting

Chamber	Pressure (mm Hg)
Right atrium	
a wave	20
v wave	20
Mean	15
Right ventricle	40/17
Pulmonary artery	
Systolic/diastolic	40/25
Mean	28
Pulmonary capillary wedge	
a wave	27
v wave	25
Mean	22
Left ventricular	170/25

Comment

Cardiac transplantation in our current series of triple-therapy patients has resulted in a survival rate of 94% for 1 year and 92% for 2 years. This patient originally started in a noncyclosporine protocol group (5-year actuarial survival, 34%) and was switched to cyclosporine because of severe osteoporosis and striking cushingoid features. She was diabetic and moderately obese and had had four rejection episodes and five episodes of serious infection. Because of her less than ideal condition at age 58 years, she was believed not to be a good candidate for retransplantation when her left main coronary artery stenosis was diagnosed. Furthermore, the 6-to-12-month waiting period for a donor for a blood type O potential cardiac recipient was believed to be prohibitive in view of her dyspnea, positive thallium stress test, and 85% left main stenosis [5].

Coronary revascularization, whether by percutaneous

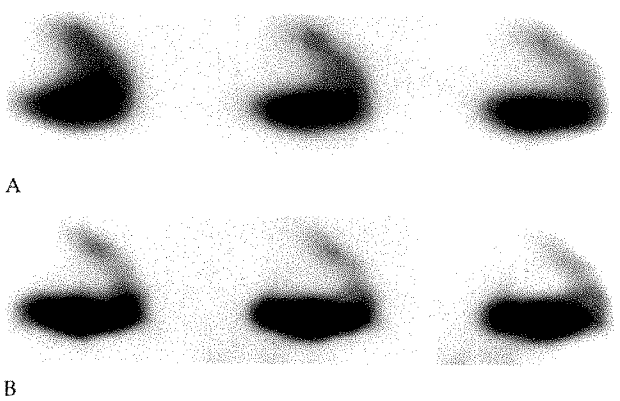

Fig 5. Exercise (A) and redistribution (B) tomographic thallium images 6 weeks after operation. An area of mild decreased perfusion is apparent along the anterior wall, but there is no evidence of reversible ischemia. No new electrocardiographic evidence of ischemia was noted during exercise.

coronary angioplasty or by coronary artery bypass grafting, is generally not applicable to most patients with graft atherosclerosis because the disease process is diffuse, involving the distal vessels, and because it is frequently rapidly progressive [2, 6, 7]. Retransplantation has been the only option available for most heart transplant recipients with severe accelerated coronary artery disease, although several cases of successful coronary angioplasty have been reported [4, 8]. Longer follow-up information is needed for better assessment of the impact of this latter approach, as is also true for this patient who underwent successful coronary artery bypass grafting.

Because of evidence of left main coronary artery disease and severe stenosis of the proximal left anterior descending and circumflex arteries, we considered percutaneous coronary angioplasty with percutaneous cardiopulmonary bypass, but with the long-term results of this technique unknown and the high risk in this patient with a previous open heart operation, this method of myocardial revascularization and protection was not pursued [9].

The pathophysiology of accelerated graft atherosclerosis is unknown, but it may involve injury during preservation or an immunological response at the endothelium of the coronary vessels, or it may be multifactorial, involving one or more known risk factors for coronary artery disease [2, 7, 10, 11]. Attempts to relate development of accelerated graft atherosclerosis with the usual risk factors associated with coronary artery disease have not been useful in the management of these patients, although lowering of serum lipids and discontinuing smoking are recommended by most researchers [1, 2, 7, 12–14]. The use of platelet inhibiting agents has also not been of proven benefit, although experimental animal work has suggested a role for platelet inhibiting agents [15, 16].

Our patient had adult-onset diabetes and systemic hypertension and was a nonsmoker. Her cholesterol and triglyceride levels were elevated, with a low level of high-density lipoprotein cholesterol at her last screening 1 year before angiographic documentation of the left main stenosis. Reports conflict, however, with regard to the value of these determinants in predicting development of accelerated graft atherosclerosis [2, 12–14].

Coronary angiography in the previous year may have precipitated development of the left main stenosis, if the left coronary catheter had irritated and denuded the endothelium, resulting in a localized hyperplastic reaction similar to that which occurs in restenosis after successful coronary angioplasty [17]. This is unlikely because the coronary stenoses of the left anterior descending and circumflex arteries had also progressed substantially.

This patient also had anatomical evidence of major constrictive pericarditis at the time of operation, with visibly significant improvement in ventricular filling after pericardiectomy. The preoperative hemodynamic measurements were obtained at an outside institution, and specific waveform data are unavailable, although the pressures may have suggested a restrictive process (Table 2). This is an important finding in view of the frequency of restrictive abnormalities observed after transplantation.

This report of successful coronary bypass grafting in a cardiac transplant recipient has shown that even high-risk patients may benefit from coronary revascularization if high-risk coronary anatomy is present or if the patient is severely symptomatic. Based on our experience and that of other investigators, we believe that coronary revascularization by either coronary bypass grafting or coronary angioplasty should be considered in patients who are at risk of sudden death or serious cardiac dysfunction while being considered for or awaiting retransplantation. Efforts at earlier identification of accelerated graft atherosclerosis are of prognostic importance and may provide time for considering current therapeutic alternatives [18]. Reducing the risk of development of coronary artery occlusive disease in heart transplant recipients and its progression during long-term follow-up is one of the most important unsolved challenges to continued improvement in longevity after successful cardiac transplantation.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 3, 1991. The closing date for registration is August 1, 1990.

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A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

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Late Left Atrioventricular Valve Insufficiency After Repair of Partial Atrioventricular Septal Defects: Anatomical and Surgical Determinants

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Risk factors for late left atrioventricular (AV) valve insufficiency, which occurred in 16 (18%) of 90 patients evaluated after repair of partial AV septal defect, were examined. The operative findings in 9 patients undergoing reoperation were also examined. Preoperative left AV valve insufficiency was significantly more common in the group with late left AV valve incompetence, as were associated valvular malformations as a whole and fenestrations of valve leaflets in particular. Conversely, the higher incidence of malformed or malpositioned papillary muscles, accessory clefts, and double-orifice left AV valves in the group with late left AV valve insufficiency did not reach significance. The method of surgical treatment of the septal commissure was not a significant factor. In the group having reoperation, additional valvular malformations were found in association with inappropriate treatment of the septal commissure in 7 patients. The 2 remaining patients had either a directly sutured ostium primum or dilatation of the annulus. Three re-repairs were successful. Five patients required prosthetic valve replacement. Preoperative left AV valve insufficiency and associated valvular malformations are major determinants of late left AV valve insufficiency in partial AV septal defect.

(Ann Thorac Surg 1990;49:111–4)

A high incidence of late left atrioventricular (AV) valve insufficiency after correction of partial AV septal defects has been reported [1, 2]. Although the degree of preoperative left AV valve insufficiency is thought to influence valve function postoperatively [1–3], very little is known about other determinants of this complication. This retrospective study investigates possible risk factors for late postoperative left AV valve insufficiency, with special emphasis on anatomical determinants and the possible influence of surgical technique.

Material and Methods

Definitions

Partial or incomplete AV septal defect [4] is defined as one with no major interventricular communications and with two separate valve orifices [5]. Following the new concepts on this malformation [6], we used the terms *left AV valve* and *right AV valve* instead of *mitral valve* and *tricuspid valve*, respectively. Also, we used the term *septal commissure* instead of *cleft* to indicate the gap between the left superior and left inferior leaflets. A double-orifice left AV valve was considered to be present when there were two separate valve orifices, each supported by a distinct subvalvular apparatus.

A fenestration or perforation of the left AV valve is an orifice, congenital or acquired in origin, well separated from the main orifice but not supported by a chordal apparatus.

Malformations or malpositions of the papillary muscles were grouped together. Malformations of papillary muscles included abnormally thick muscles with rudimentary or absent chordal apparatuses inserted directly into the undersurface of the leaflets and multiple thin muscles with abnormal insertions into the ventricular walls. Anomalous positions of the papillary muscles are very common in AV septal defect and are very difficult to classify. Therefore, only extreme malpositions, ie, potentially parachute mitral valve [7] or extreme lateralization of the papillary muscles, were considered.

Accessory clefts or commissures, defined as radial openings from the free edge of a leaflet, were complete (up to the annulus) or incomplete (partially splitting the leaflet).

Late left AV valve insufficiency was defined as such because it was not evident at the end of the operation.

Patient Population

From 1968 to June 1986, 107 patients underwent repair of partial AV septal defect at the Division of Cardiac Surgery, Ospedali Riuniti di Bergamo. Age at operation ranged from 10 months to 39 years with a mean age of 8.3 years. Fifteen additional patients, in whom the partial AV septal defect was part of a complex malformation, were excluded from this study.

Four patients (3.7%) died within 30 days after operation, and 13 patients were subsequently lost to follow-up. The remaining 90 patients (87.4%) were followed 18 months to 18 years postoperatively. During follow-up,

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Table 1. Anatomical and Surgical Risk Factors for Late Left Atrioventricular Valve Insufficiency

	Total Group (n = 90)			Left AV Valve Insufficiency Group (n = 16)			
Risk Factor	No.	%	70% CL	No.	%	70% CL	*p* Value
Significant							
Associated valvular malformations (all)	26	28.9	23.7–34.6	9	56.2	40.4–71.1	0.032
Fenestrations of valve leaflets	2	2.2	0.7–5.2	2	12.5	4.2–27.1	0.046
Not significant							
Malformed/malpositioned papillary muscles	13	14.4	10.5–19.3	5	31.2	18.1–47.3	0.099
Accessory clefts	6	6.7	4.0–10.6	2	12.5	4.2–27.1	0.42
Double-orifice left AV valve	5	5.6	3.1–9.3	1	6.2	0.8–19.7	0.91
No suture in septal commissure	28	31.1	25.8–36.9	5	31.2	18.1–47.3	0.99

AV = atrioventricular; CL = confidence limits.

major left AV valve insufficiency that was not evident at the end of the operation developed in 16 patients (17.8%). The degree of valvular incompetence was assessed using clinical, roentgenographic, echocardiographic, and, when available, angiographic criteria. Only moderate or severe left AV valve insufficiency was considered relevant for this study.

Twenty-six (28.9%) of the 90 patients were known to have additional malformations of the left AV valve apparatus. A double-orifice valve was present in 5 patients (5.6%), fenestrations of valve leaflets in 2 (2.2%), malformed or malpositioned papillary muscles in 13 (14.4%), and accessory clefts in 6 (6.7%).

During the study period, the surgical treatment of the septal commissure varied. The commissure was sutured in 62 patients (68.9%) and was left open in 28 (31.1%).

These anatomical and surgical variables were considered possible risk factors for the occurrence of late left AV valve insufficiency. They were examined for significance with the usual statistical methods, including calculation of the *p* value by the χ^2 and Fisher's exact tests, and by looking at the overlapping and nonoverlapping distribution of the 70% confidence limits. Specifically, all the following variables were tested: age at operation; weight at operation; year of operation; preoperative left AV valve insufficiency (assessed according to the previously described criteria); associated valvular malformations; double-orifice left AV valve; fenestrations of valve leaflets; malformed or malpositioned papillary muscles; accessory clefts; and surgical management of the septal commissure.

During the same time frame, 13 reoperations for severe left AV valve dysfunction after repair of partial AV septal defect were performed on 9 patients, 2 of whom had originally been operated on elsewhere. The findings at reoperation were also retrospectively analyzed in an effort to assess potential surgical causes of late left AV valve insufficiency.

Results

Age and weight at the time of repair were not significantly different in the group with late left AV valve incompetence compared with the overall study group, nor was the year of operation. Preoperative left AV valve insufficiency was present in 13 (81.25%) of the 16 patients with late left AV valve insufficiency and in 46 (51.1%) of the 90 patients in the total study group. It represented the single most significant risk factor for late left AV valve insufficiency ($p = 0.025$).

Associated valvular malformations as a group significantly increased the risk of late left AV valve insufficiency. They were present in 56.2% of the 16 patients with late insufficiency and in 28.9% of the total study group ($p = 0.032$) (Table 1). Each malformation was found more frequently in the group with late left AV valve insufficiency compared with the total study group. Although the higher incidence of double-orifice left AV valve (6.2% versus 5.6%) was negligible, that of accessory clefts (12.5% versus 6.7%) and of malformed or malpositioned papillary muscles (31.2% versus 14.4%) was more relevant, and that of fenestrations of valve leaflets (12.5% versus 2.2%) reached significance ($p = 0.046$) (see Table 1).

Surgical treatment of the septal commissure (suturing or leaving it open) did not influence the incidence of late left AV valve insufficiency (see Table 1).

At reoperation, the cause of left AV valve dysfunction was identified in each of the 9 patients. Inappropriate suturing of the septal commissure resulted in valvular stenosis and insufficiency in 2 patients with a double-orifice left AV valve. In 3 patients with malpositioned papillary muscles, the suturing of the septal commissure impeded the excursion of the reconstructed left AV valve. Conversely, the suture in the septal commissure had dehisced in 2 patients in whom extreme lateralization of the papillary muscles had put excessive tension on the suture line. In 1 patient, isolated dilatation of the annulus was the cause of left AV valve insufficiency, and in another patient, a directly sutured ostium primum caused severe valvular displacement.

Re-repairs were performed after the causes of regurgitation were assessed. Dilatation of the annulus was successfully treated with a Wooler-Kay annuloplasty. When indicated, the septal commissure was resutured after the leaflet edges were unfurled or the papillary muscles were split, or both. An attempt to reopen the sutured septal commissure in a double-orifice left AV valve was not successful and necessitated prosthetic valve replacement. Prosthetic valve replacement was ultimately performed in 5 patients with one death. The other 4 patients in the group having reoperation underwent valve re-repair also with one death. Both deaths occurred in patients in New York Heart Association class IV and were due to irreversible low-output syndrome.

Comment

Partial AV septal defect is a malformation that is often overlooked. Surgical repair is mandatory for all patients with this condition, for its natural history leads to progression of left AV valve regurgitation, serious dysrhythmias, pulmonary vascular obstructive disease, and eventually death (usually in the fourth or fifth decade) [8].

Large surgical series show operative mortalities as high as 10% [1], and the operative mortality of 3.7% in our series is certainly not negligible. Late results are affected by the large number of failures of left AV valve repair, leading to reoperation or late death. In a series from Boston [1], 8 (10%) of 83 survivors of the initial operation required reoperation for moderate or severe left AV valve regurgitation, with three deaths. Ten of 19 late deaths among 258 traced patients who survived initial repair of AV septal defect (all types) at The University of Alabama occurred in patients known to have failure of the left AV valve repair [2].

The aim of our analysis was to identify possible risk factors for the occurrence of late left AV valve insufficiency which can lead to reoperation. Through the operative findings at reoperation and the techniques of re-repair, we also attempted to identify possible surgical errors and their remedies.

As in other reports [1, 2, 6, 9], our analysis indicates that preoperative left AV valve insufficiency is the single most significant risk factor for the occurrence of this condition postoperatively (ie, failure of the valve repair). The AV valve apparatus is malformed in AV septal defect, and an incompetent left AV valve is present in a large percentage of patients [1, 2]. In our series, moderate or severe left AV valve insufficiency was present preoperatively in 46 (51.1%) of 90 patients.

Carpentier [6] recognized the complexity of this malformation, which involves all components of the valve, and suggested it be considered a three-leaflet valve and repaired accordingly. He indicated that the repair should not be stereotyped, but rather should be performed after careful assessment of all components and should consist of individualized plastic procedures.

Based on these concepts, we investigated the additional malformations of the valvular apparatus potentially leading to failure of the valve repair. In our analysis, all types of additional valvular malformations seemed to increase the incidence of late left AV valve insufficiency except perhaps the presence of a double-orifice left AV valve.

A double-orifice left AV valve was present in 5.6% of our patients and in 4.3% of patients with all types of AV septal defect in the Mayo Clinic experience [10]. This malformation should be handled conservatively, and nothing should be done to the valve when the malformation does not cause valvular regurgitation. When severe valvular insufficiency is present, it is usually located at the level of the septal commissure. In these cases, partial closure of the septal commissure, thus avoiding subsequent valvular stenosis, might be the treatment of choice [10]. In fact, Kirklin [2] believes that the adverse effect of double-orifice left AV valve may be due to its tendency to narrow the valve orifice. Alfieri and Demole [11] recently suggested that repair of a severely insufficient double-orifice left AV valve be accomplished by transforming it into a triple-orifice valve. This technique avoids the risk of restricting the total valve area too much.

Accessory clefts were found in all three leaflets of the left AV valve; their treatment was individualized based on valve function. Even though they were more frequently found in the group with late left AV valve insufficiency, their adverse influence was not significant.

The role of malformed or malpositioned papillary muscles in altering the mechanics of the left AV valve in AV septal defect has been recognized by Carpentier [12] and is suggested by our findings. It remains unclear which specific alterations of the papillary muscles prevent adequate late valve function. The small numbers in our series did not allow further subdivision of papillary muscle morphologies and locations.

Fenestrations (or perforations) of the valve leaflets have been previously reported [13]. The 2 cases in our series were both associated with late left AV valve insufficiency. A congenital origin is doubtful, but no evidence of previous bacterial endocarditis was found in either patient. At the time of repair, valvular incompetence was not demonstrated, and the leaflets were therefore left untouched. Even though neither patient has yet required reoperation, we now advise patch closure of all fenestrations whether valvular insufficiency is present or not.

In an attempt to respect the three-leaflet anatomy of the left AV valve, we have avoided routine closure of the septal commissure since 1978. In making decisions in regard to this problem, we consider the following: degree and location of the left AV valve insufficiency; size of the lateral leaflet [14]; anatomy and position of the papillary muscles; and the presence of a double-orifice left AV valve. In this series, we could not clearly identify an adverse effect of closure of the septal commissure per se on late valve function.

At reoperation, only one instance of failure of the repair could be positively attributed to a faulty procedure (direct closure of an ostium primum). In this patient, severe valvular distortion prevented an adequate re-repair and necessitated prosthetic valve replacement. The dilatation of the annulus found in another patient was presumably not related to the previous surgical technique; this patient underwent successful re-repair. Inappropriate suturing of the septal commissure was associated with failure of the repair in 7 patients. However, simply leaving the septal commissure untouched at the time of the original repair would have resulted in severe left AV valve insufficiency in each of them. In fact, the adverse interaction of the anatomical factors already mentioned was evident in all, and reassessment of the anatomy and physiology of the valve in light of our improved knowledge prompted more complex re-repairs that were successful in only 2 patients.

In summary, additional valvular malformations play a major role in preventing the long-term success of valve repairs in partial AV septal defect. An improved awareness of these variations leads to individualized repairs that promise better long-term valve function.

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Retrospective Analysis of the Efficacy of Open Lung Biopsy in Acquired Immunodeficiency Syndrome

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Open lung biopsy (OLB) was performed on 66 patients with acquired immunodeficiency syndrome from November 1981 through December 1987. Twenty-two patients with severe respiratory failure died within a month, 3 during operation. Fourteen patients with negative transbronchial biopsy and 19 with failure of treatment based on transbronchial biopsy died within a year. Six were alive and 5 were lost to follow-up. The most common organism found in patients with severe respiratory failure was *Pneumocystis carinii* alone or with other pathogens. Successful therapeutic change based on OLB findings was possible in only 1 (1.5%) of the 66 patients. Open lung biopsy has limited application in the management of acquired immunodeficiency syndrome. In patients with overt pulmonary failure, OLB is invariably fatal. Those seen with suspicious lung infiltrates without risk factors or with known risk factors and negative transbronchial biopsy results might benefit from OLB. In our institution, 18 of 64 acquired immunodeficiency syndrome admissions underwent OLB in 1983, whereas in 1987, only 2 of 302 patients admitted with acquired immunodeficiency syndrome had OLB.

(Ann Thorac Surg 1990;49:115–7)

The acquired immunodeficiency syndrome (AIDS) is an immunity disorder that leads to the development of opportunistic infections and malignant tumors. Pulmonary involvement is the more frequent manifestation of the syndrome and is characterized by diffuse bilateral infiltrates, shortness of breath, fever, and hypoxia [1, 2]. Spontaneous pneumothorax is increasingly seen as the initial presentation in our institution [3]. Finding the agents that cause pulmonary disease in AIDS is a diagnostic challenge for thoracic surgeons and other pulmonary specialists. Bronchoalveolar lavage, transbronchial biopsy, and open lung biopsy (OLB) are the procedures most commonly used to diagnose opportunistic organisms in these patients. This study is a retrospective review of 66 consecutive patients with AIDS who underwent OLB; it was undertaken in an attempt to identify those cases in which this procedure might be justified.

Material and Methods

Sixty-six patients with AIDS who underwent diagnostic OLB from November 1981 through December 1987 were reviewed. These included 62 male and 4 female patients ranging in age from 6 months to 57 years (mean age, 37 years). During this period, 779 patients with AIDS were admitted to St. Vincent's Hospital and Medical Center in New York City.

Patients submitted to OLB belonged to one of the following groups: (1) 22 patients not considered candidates for endoscopy because of severe respiratory failure; (2) 25 patients shown to have *Pneumocystis carinii* (PC) at bronchoscopy that had not responded to therapy; (3) 19 patients submitted to OLB because transbronchial biopsy had failed to provide a diagnosis. The technique for performing OLB was the same on all patients: with the patient in the supine position, under general endotracheal anesthesia, the lung most involved by infiltrates underwent operation. A 5-cm-long inframammary incision was performed and the chest cavity was entered through the divided intercostal muscle. A small wedge of lung was exteriorized and resected. The area of resection was repaired with sutures or staples. A chest tube was inserted along the anterior axillary line in the fifth intercostal space. The tissue was submitted for touch preparation, permanent sections, and viral, bacterial, and fungal cultures.

Results

Of 66 patients who underwent OLB, 5 were lost to follow-up and 6 were alive. Fifty-five patients died (overall mortality, 83%). The longest survivor was alive 33 months after biopsy (mean, 3.4 months). The most common diagnosis was PC alone or in combination with other pathogens as shown on the following list:

Pneumocystis carinii	49
Cytomegalovirus	4
Kaposi's sarcoma	3
Cryptococcus	3
Legionella	3
Lymphoma	3
Pneumonitis	3
Listeria	1
Mycobacterium	1

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Group 1

These patients were operated on early in our experience. Sixteen of the 22 patients with severe respiratory failure were found to have PC. Treatment based on study of tissue obtained by OLB did not change the fatal course of the disease. All patients succumbed within a month of irreversible pulmonary failure and profound hypoxia. Three patients died during operation.

Group 2

Twenty-five open lung biopsies performed on patients found to have PC that had not responded to appropriate treatment corroborated the early endoscopy findings and failed to contribute to any change in therapy.

Group 3

Diagnosis made from tissue obtained by OLB from 19 patients with previous negative bronchoscopy allowed change in treatment in only 3 cases. One female patient without risk factors treated for chronic pneumonitis without success showed PC on OLB. She then received proper therapy and was alive 2 years later at the time this study was completed. One patient empirically treated for PC showed mycobacteria on OLB, and another treated for tuberculosis showed PC. Both patients died of progressive respiratory failure despite the institution of appropriate medication. To this group belonged 3 patients with Kaposi's sarcoma (KS). These patients are of interest because they all had KS skin lesions proved by biopsy. In addition, one of them had gastrointestinal KS. All 3 patients died of their disease without responding to treatment.

Comment

Since 1979, patients with a new clinical picture were seen in the United States [1, 2, 4]. This syndrome was detected in "risk groups": homosexual and bisexual men, intravenous drug abusers of both sexes, and hemophiliacs (patients requiring numerous blood transfusions). The victims were found to suffer not only from infections caused by opportunistic organisms, but also from lymphoma and Kaposi's sarcoma. These conditions were previously detected in immunosuppressed patients (patients receiving transplants or chemotherapy) [5]. The entity now known as acquired immunodeficiency syndrome (AIDS) has been detected in almost every country in the world and has taken on epidemic proportions [6]. Thoracic diseases caused by microorganisms and tumors in AIDS patients have been extensively described [1, 4, 7]. The thoracic surgeon or pulmonary specialist is responsible for establishing a diagnosis promptly and accurately, because early therapy might prevent uncontrollable complications of infections caused by opportunistic organisms. Three diagnostic modalities are used to evaluate pulmonary pathology: bronchoalveolar lavage, transbronchial biopsy, and open lung biopsy. These techniques have been amply discussed in the literature [2, 8–10].

Our experience corroborates with what has been found by other authors: transbronchial biopsy combined with bronchoalveolar lavage is the safest and more expeditious diagnostic procedure for AIDS pneumonitis [10]. In collective reviews, these procedures established the diagnosis of PC pneumonitis in 95% of the cases and of *Mycobacterium avium* in 78% [11]. Transthoracic fine-needle aspiration has also been used for diagnosis of opportunistic infections [12]. The indication for OLB has then been reserved for those cases in which bronchoscopy was not diagnostic, when there were contraindications to bronchoscopy (coagulopathy or severe pulmonary failure), or when there was no response to treatment based on previous bronchoscopic findings [2, 10, 13] (Fig 1).

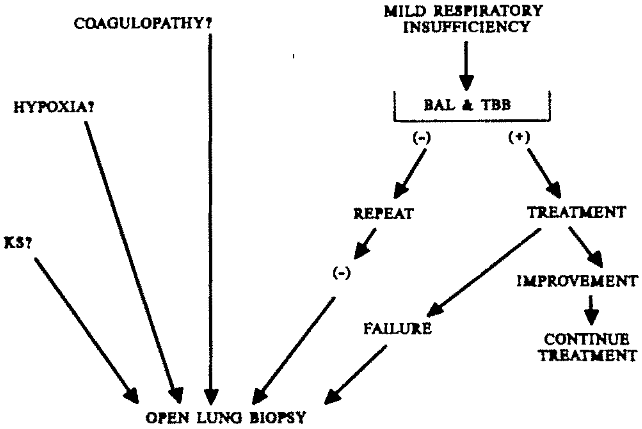

Fig 1. Strategy to follow when pulmonary pathology is suspected in a patient with AIDS. Positive and negative signs *refer to the diagnosis of opportunistic organisms.* Question marks *are placed next to those indications that carried the highest mortality.* (BAL = *bronchoalveolar lavage;* KS = *Kaposi's sarcoma;* TBB = *transbronchial biopsy.)*

Whenever OLB is contemplated, two questions are raised: (1) Should one submit the patient to a painful and dangerous procedure when it is known that it will have little influence on survival; and (2) Should one expose operating room personnel to the accidental transmission of AIDS? Our experience shows that OLB did not contribute to survival in two of the three groups of patients and did in only 1 (1.5%) of the 19 patients in group 3.

Particularly ominous was the result of OLB on patients who had severe hypoxia preoperatively. Three of these patients died on the operating room table, and the remainder died within a month. Among those patients operated on because of failed treatment based on bronchoscopy, OLB did not yield any information to allow therapeutic changes that could have altered the course of the disease. In the group that underwent OLB because of nondiagnostic bronchoscopy, only 3 patients showed any benefit, and despite appropriate treatment, 2 died of progressive respiratory failure.

Open lung biopsy has been reported to be the procedure of choice to diagnose pulmonary KS [6, 10, 13]. In our series, the 3 patients suspected of having pulmonary KS showed KS of the skin, and 1 had KS of the gastrointestinal tract. Open lung biopsy revealed the same entity in the lung. All 3 patients failed to respond to treatment and died. We believe that open lung biopsy for diagnosis of KS should not be recommended for those patients with proven KS lesions elsewhere.

The danger of exposure to the AIDS virus must be a serious concern for members of the operating room staff. Recommendations for the prevention of transmission of this virus state that health care workers should consider all patients as potentially infected. They further outline strict measures to be followed routinely when invasive procedures, such as OLBs, are performed [14]. Despite these strict measures, accidental injury to the skin or mucosal membranes can occur.

This study shows that the place for OLB in the management of AIDS is quite limited. This procedure should not be performed on patients with overt pulmonary failure because the outcome is inexorably fatal. Of 64 AIDS admissions to our institution in 1983, 18 underwent OLB, whereas in 1987, of the 302 admissions with AIDS, only 2 had OLB. However, in those patients without risk factors who have suspicious pulmonary infiltrates and negative transbronchial biopsy results, OLB might be of benefit.

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Disruption of the Aortic Anastomosis After Heart-Lung Transplantation

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Disruption of the aorta at the anastomotic site occurred in 4 of 66 consecutive heart-lung transplant recipients and was associated with a 100% mortality. In 3 of these patients, *Candida* either was cultured from the suture line or was seen in the wall of the aorta at postmortem examination. In 2 of these 3 patients, cultures of material from the donor trachea taken at the time of explantation grew *Candida* species. Two patients were seen with sudden massive hemorrhage on postoperative day 26 and postoperative day 28. One patient experienced acute decompensation due to right ventricular outflow tract obstruction on postoperative day 30, and the remaining patient was seen 7 months postoperatively with obstruction of both the left main bronchus and the right pulmonary artery caused by extrinsic compression by an aortic pseudoaneurysm. A high index of suspicion should be maintained when transplanting lungs containing *Candida* species, as we believe there is substantial evidence of donor transmission of the fungal agents. We now include amphotericin B in our antibiotic prophylactic regimen in an attempt to prevent fungal infection because previous treatment has been uniformly unsuccessful. Furthermore, we wrap both the trachea and the aorta with omentum to lessen the likelihood of mediastinal spread of infection to the aortic suture line.

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Serious complications after cardiopulmonary transplantation continue to occur in a substantial number of patients, and result in a disappointingly high mortality [1, 2]. Recipients of heart-lung allografts appear uniquely predisposed to perioperative infections of the lungs and the mediastinum [3].

We encountered anastomotic disruption of the aorta in 4 of 66 consecutive recipients, and believe this complication is related to infection along the aortic suture line, spread from the open-ended donor trachea at the time of operation. We report here our experience with this unusual complication after cardiopulmonary transplantation, and stress the varied and often confusing presentations, possible treatment strategies, and the likely association with *Candida* species present in the donor trachea.

Material and Methods

Between May 1982 and September 1988, 66 patients received 68 cardiopulmonary transplants at the University Health Centers of Pittsburgh. The average age was 32 years with a range of 3 to 51 years. There were 26 (39%) male and 40 (61%) female patients.

Surgical Technique and Prophylaxis

Selection of donors was based on the following criteria: negative history of primary pulmonary disease, clear serial radiographs of the lungs, absence of neutrophils or abundant bacteria on Gram stain of sputum, arterial oxygen tension greater than 300 mm Hg on an inspired oxygen fraction of 1.0, appropriate size match, and absence of heavy secretions on bronchoscopy. Sixty-seven percent of donors received systemic antibiotics, usually a first-generation cephalosporin.

The distal trachea of the recipient was sutured to the donor airway at a level two to three cartilaginous rings above the carina. Dissection of the recipient proximal trachea was avoided to reduce the risk of compromising the blood supply to the anastomosis. The recipient tracheobronchial tree was lavaged with 10% povidone-iodine solution through the endotracheal tube before division of the airway in an attempt to reduce contamination of the mediastinum from the airway.

The donor trachea, which had been closed with staples at its midportion during procurement, was opened and trimmed to the level of the carina. The airways were lavaged with normal saline solution in an attempt to remove by suction any accumulated secretions. A swab (Culturette, modified Stuart's transport medium; American Scientific Products, Obetz, OH) of the donor trachea was sent for aerobic and fungal cultures. We used 4-0 Prolene (Ethicon, Somerville NJ) suture for the tracheal anastomosis and since 1986 have interrupted the tracheal anastomosis in three places. The tracheal anastomosis was encircled with a wrap of omentum, brought up anteriorly through an extension of the midline incision. The aortic anastomosis was completed with a continuous suture of 4-0 Prolene.

Between 1982 and 1986, recipients received perioperative antibiotic prophylaxis consisting of intravenous ad-

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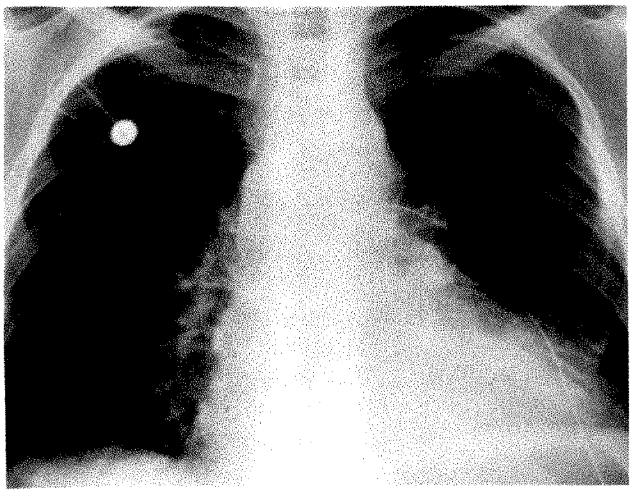

Fig 1. (Patient 1.) Normal chest roentgenogram made hours before aortic disruption.

ministration of cefamandole nafate. Since 1986, recipients have received clindamycin in addition to cefamandole. None of the recipients in this study received antifungal agents as part of the prophylactic regimen. Antibiotic therapy was individualized and continued after 48 hours only if there was evidence of pulmonary infection.

Case Histories

PATIENT 1. A 21-year-old man with a history of primary pulmonary hypertension underwent cardiopulmonary transplantation on December 20, 1986. An omental wrap was placed around the trachea. Lung preservation was with hypothermic flush. Bacterial and fungal cultures grown from material from the donor trachea were sterile. The immediate postoperative course was uncomplicated. The patient was extubated on postoperative day 4 and two days later was transferred from the intensive care unit. The chest roentgenograms showed normal lungs and mediastinum on postoperative day 26, the morning of expected discharge from the hospital (Fig 1). Later that morning, the patient suddenly became hypotensive and died despite all attempts at resuscitation.

Postmortem examination revealed a disruption of the aortic anastomosis with an intact continuous 4-0 Prolene suture. Although there was no evidence of mediastinal abscess or false aneurysm, yeast forms consistent with *Candida* were observed in the aortic wall at the level of the anastomosis. No evidence of candidiasis was noted elsewhere at autopsy.

PATIENT 2. A 39-year-old woman with primary pulmonary hypertension underwent cardiopulmonary transplantation on November 13, 1986. A single omental wrap was placed around the trachea and aorta. Lung preservation was with hypothermic flush. Cultures grown from material from the donor trachea produced only coagulase-positive staphylococci. Fungal cultures were negative. The postoperative course was unremarkable.

Seven months postoperatively, the patient was admitted with a 3-week history of cough and shortness of breath. Roentgenograms of the chest showed collapse of the left lower lobe. Bronchoscopy and tomograms revealed a tapered closure of the left main bronchus, which was thought to be due to ischemic injury to the airway. Computed tomograms of the mediastinum were initially interpreted as normal.

A silicone stent was placed in the left main bronchus. Two days later, the patient became profoundly hypoxic and at emergency bronchoscopy, the stent was noted to have migrated proximal to the area of narrowing of the left main bronchus. A ventilation/perfusion scan showed a decrease in perfusion to the right lung and a decrease in ventilation to the left lung. A pulmonary arteriogram demonstrated extrinsic compression of the intrapericardial right pulmonary artery (Fig 2). The levophase of the pulmonary angiogram demonstrated a large ascending aortic pseudoaneurysm (Fig 3). Reevaluation of the computed tomographic scans of the mediastinum confirmed the likely presence of an aneurysm.

At reexploration, a 6-cm aortic pseudoaneurysm was found. It arose from the posteromedial aspect of the aortic anastomosis and had eroded the anterior portion of the left main bronchus. The aneurysm was confined in part by the omental wrap, which included the aortic anastomosis. The left main bronchus was deemed irreparable and was ligated, as was the left pulmonary artery. The disrupted aortic anastomosis along with an intact 4-0 Prolene sture was excised, and the repair was completed using an interpositioned aortic homograft. However, the patient died in the operating room of excessive bleeding and cardiopulmonary failure. Bacterial and fungal cultures of material from the mediastinum and the aortic wall were sterile, and histological staining of the pseudoaneurysm failed to show any organisms.

PATIENT 3. A 25-year-old woman with primary pulmonary hypertension underwent cardiopulmonary transplanta-

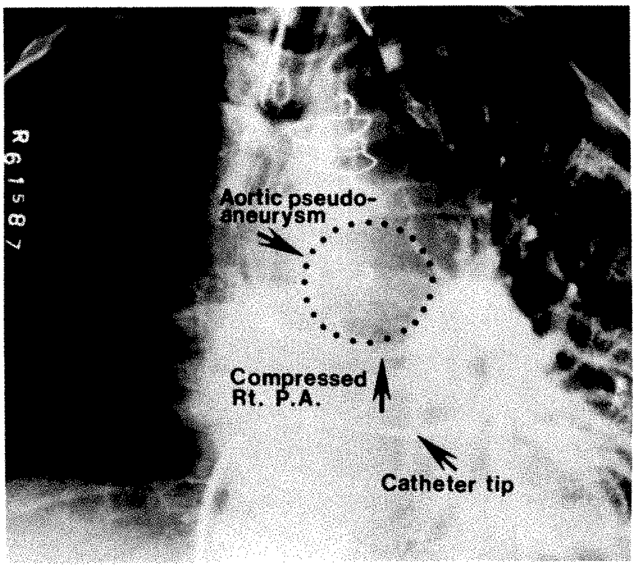

Fig 2. (Patient 2.) Pulmonary angiogram with tip of catheter in main pulmonary artery. Pseudoaneurysm is nearly completely compressing the right pulmonary artery (P.A.).

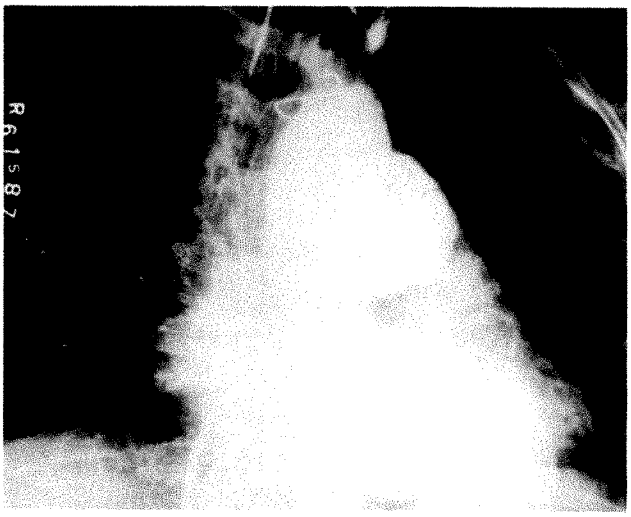

Fig 3. (Patient 2.) Levophase of the pulmonary angiogram demonstrates the presence of a large aortic pseudoaneurysm.

tion on June 10, 1987. Lung preservation was with hypothermic flush. Bacterial cultures of material from the donor trachea grew β-hemolytic streptococci, coagulase-positive staphylococci, *Acinetobacter anitratus*, and *Klebsiella*. Fungal cultures were negative. Postoperatively, a *Pseudomonas* pneumonia developed and failed to resolve despite aggressive therapy.

The patient underwent a second heart-lung transplantation on postoperative day 10. The omental wrap developed at the time of the first transplantation was not suitable for use in the second operation. Fungal cultures of material from the donor trachea grew heavy *Candida albicans*. The patient made a slow but progressive recovery until the 28th day after the second transplantation, when she sustained a cardiac arrest and could not be resuscitated. Postmortem examination revealed a disruption of the ascending aortic anastomosis with a large right hemothorax. Histological examination of the aortic wall at the level of the anastomosis revealed the presence of a pseudoaneurysm (Fig 4) and pseudohyphae typical of *Candida* (Fig 5).

PATIENT 4. A 38-year-old man with a history of primary pulmonary hypertension underwent cardiopulmonary transplantation on December 4, 1987. Lung preservation was with hypothermic flush. An omental wrap was placed around the trachea. Bacterial cultures of material from the donor trachea grew coagulase-positive staphylococci and fungal cultures grew *Candida stellatoidea*. The initial postoperative course was complicated by *Haemophilus influenza* pneumonia and later by a wound and pleural space infection caused by *Mycoplasma hominis*. Both resolved with therapy.

One month after the operation, the patient became acutely dyspneic and hypotensive. He was transferred to the surgical intensive care unit where a pulmonary artery catheter was placed. It showed a right ventricular systolic pressure of 80 mm Hg with normal pulmonary artery pressures. Right ventricular outflow tract obstruction by a false aneurysm of the aorta was further suggested by the acute angle made by the passage of the pulmonary artery catheter from the right ventricle into the pulmonary artery.

At emergency reoperation, repair of an aortic pseudoaneurysm with an interpositioned aortic homograft was performed. Cultures of material from the aortic wall at the level of the anastomosis grew *C stellatoidea*, the same species grown from the donor trachea. *Candida* was also seen on histological examination of the inflamed aortic wall. In spite of treatment with amphotericin B, the patient never overcame the effects of the perioperative shock, and irreversible renal and hepatic failure devel-

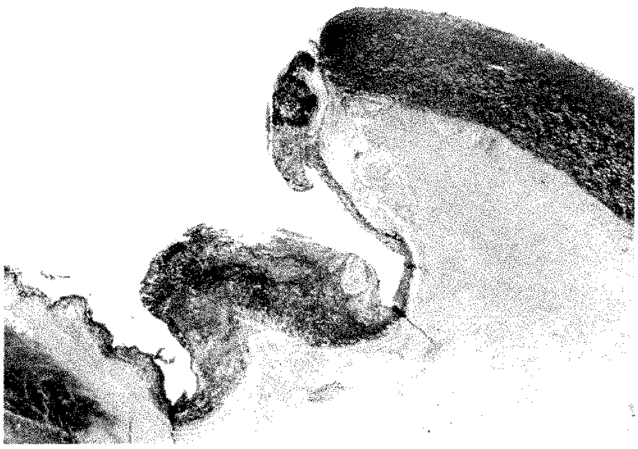

Fig 4. (Patient 3.) Elastic tissue stain highlights the mycotic pseudoaneurysm of the aorta. At upper right is the normal aortic elastica, which becomes inflamed and fragmented as the fibrous wall of the pseudoaneurysm expands at lower left. (Elastic van Gieson's; ×10 before 45% reduction.)

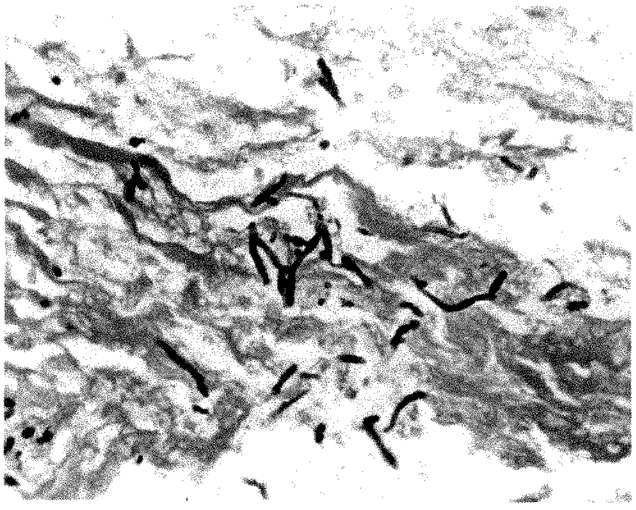

Fig. 5. (Patient 3.) Within the wall of the aorta were large aggregates of pseudohyphae typical of Candida *(Grocott; ×500 before 45% reduction.)*

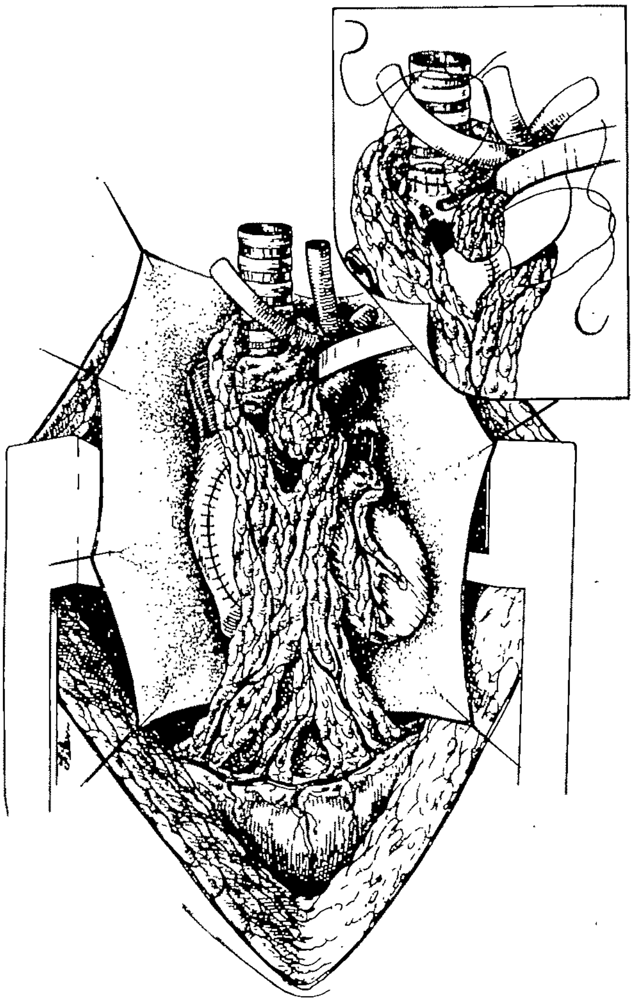

Fig 6. Omental wrap modified to include both the aortic and tracheal anastomosis.

oped. The postmortem examination demonstrated *Candida* in the aortic homograft.

Comment

In our experience, disruption of the aortic anastomosis has occurred in 4 (6%) of 66 heart-lung transplant recipients and in only 2 (0.4%) of 474 heart transplant recipients. In the heart transplant recipients, 1 case was due to disruption of the aortic suture and the other was associated with bacterial mediastinitis. Three of the four aortic disruptions that occurred in heart-lung transplant recipients arose as a result of fungal infection of the aortic suture line. The increased incidence of this complication in this patient population is probably due to the additional operative contamination by open airways, the extensive mediastinal dissection, and the slow postoperative healing of the tracheal suture line. Fungal infections may also have been encouraged by transmission of fungus from the donor to an immunosuppressed recipient and by perioperative use of broad-spectrum antibacterial agents.

Development of a mycotic aneurysm due to *Staphylococcus* in a single patient after heart-lung transplantation has been reported recently by another group [4]. Tazelaar and Yousem [5] recently reported the autopsy findings of 20 heart-lung transplant recipients, and noted three instances in which *Candida* was found at the aortic anastomosis. Two of these 3 cases were associated with a *Candida* infection of the tracheal anastomosis. One death among these 3 patients was due to bronchopneumonia, and the other two deaths were due to *Candida* sepsis.

Since 1985, we have routinely performed a Gram stain and grown aerobic and fungal cultures of material from the trachea of lung donors. We [6] reviewed the results of these culture studies to investigate the possibility of transmission of infection from the donor to the recipient. Despite adherence to strict criteria for acceptance of lung donors, 76% (28/37) of cultures gew organisms and 22% (8/37) grew *Candida* species. Pathogenic bacteria were isolated in 19 (68%) of 28 positive cultures. Oropharyngeal flora was isolated in 13 (46%) of 28 positive cultures. The presence of mouth flora was associated with a significantly increased risk of development of bacterial pneumonia in the first 2 postoperative weeks ($p = 0.004$, Fisher's exact test).

In the three instances in which a heavy growth of *Candida* species was isolated from the donor trachea, invasive candidiasis developed in the recipient. In two of these instances, cultures of material from the recipient grew the same species of *Candida* isolated from the donor trachea. We believe this evidence strongly supports donor-transmitted fungal infection. One of the patients (patient 2) did not show evidence of fungal infection at postmortem examination, and the donor tracheal fungal culture was negative. There were no technical complications identified, and the patient was not seen until the seventh postoperative month. This case may represent resolved mediastinal infection that resulted in injury to the aortic wall, thus predisposing to rupture. Cultures of material from the donor trachea in patient 1 did not grow fungus. The timing of aortic rupture suggests development of fungal aortitis in the perioperative period. In this instance, the donor tracheal culture may represent a false-negative result or spread of the organism through the bloodstream.

The clinical presentation in our patients varied. Two of the patients had an uncomplicated postoperative course until the sudden development of massive hemorrhage. One patient was seen with acute decompensation due to right ventricular outflow tract obstruction by the aortic aneurysm, and the other was seen with symptoms secondary to right pulmonary artery obstruction and partial occlusion of the left main bronchus. Three of the 4 patients were seen in the fourth postoperative week (postoperative days 26, 28, and 30). None of the patients had any clinical evidence of infection.

Because of the insidious progression and sudden presentation of this disease, both medical and aggressive surgical therapy were ineffective. Therefore, we have altered our prophylactic treatment to include systemic amphotericin B. After a test dose of 1 mg intravenously, the daily dose is gradually increased to 0.3 mg/kg/day and continued for the first 2 weeks postoperatively. In the event of renal toxicity, administration of amphotericin is discontinued until the return of renal function. In instances in which the donor tracheal cultures grow heavy

Candida species, treatment with amphotericin B is continued up to a maximum total dose of 1 g.

In summary, aortic disruption occurred in 4 of 66 heart-lung transplant recipients and was associated with a 100% mortality. In 3 of these patients, *Candida* was found at the aortic suture line and was considered to be the responsible agent. We believe that a high index of suspicion should be maintained in those patients receiving allografts infected with *Candida* and that prophylactic treatment of all recipients with amphotericin B is indicated to help prevent this complication. We believe an omental wrap should be performed in every instance. We now split the omentum and perform separate wraps of the tracheal and aortic anastomosis (Fig 6). This provides vascularized tissue between the aorta and trachea that might be of some benefit in lessening the mediastinal spread of infection and potentially containing a rupture of the aortic anastomosis.

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Effect of Circulatory Assist Devices on Stunned Myocardium

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We studied the effects of mechanical circulatory assist devices on left ventricular oxygen consumption, the integrals of systolic left ventricular wall stress (SSI), and end-systolic elastance (Ees) in 8 sheep after 25 minutes of global ischemia. Extracorporeal membrane oxygenation at 35 mL/kg/min, intraaortic balloon counterpulsation, and an intraaortic double-balloon pump were studied alone or in combination. Left ventricular oxygen consumption, SSI, and Ees were measured before and during mechanical circulatory assistance. Left ventricular oxygen consumption was calculated from transit-time measurements of left main coronary artery blood flow and fiberoptic measurements of coronary sinus blood oxygen saturation. Three pairs of sonomicrometry crystals placed across three orthogonal ventricular axes were used to calculate instantaneous ventricular volumes and pressure–volume loops from which the SSI data were derived. The Ees was measured using a new single-beat aortic occlusive method. Extracorporeal membrane oxygenation alone increased SSI and did not change Ees in postischemic poorly contracting hearts. Intraaortic balloon counterpulsation alone significantly reduced SSI and increased Ees. The combination of extracorporeal membrane oxygenation and either the intraaortic balloon pump or the intraaortic double-balloon pump reduced SSI, increased Ees, and reduced left ventricular oxygen consumption. In postischemic dilated, poorly contracting hearts, the combination of extracorporeal membrane oxygenation and intraaortic balloon counterpulsation has important advantages over extracorporeal membrane oxygenation alone.

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Mechanical circulatory assist devices used in parallel with the native heart circulate blood but also affect function of the native heart. The tacit assumption that mechanical circulatory assist devices reduce the work of the native heart, particularly if the native heart is diseased or injured, may or may not be true if the native heart continues to pump. The present studies were designed to compare the ability of various parallel (partial) mechanical assist devices to reduce left ventricular oxygen consumption and systolic load in ovine hearts after ischemic injury.

Material and Methods

Eight healthy Dorsett sheep (mean weight, 35.1 ± 3.9 kg) were studied in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). Two operations, both with Pentothal (thiopental sodium) (25 mg/kg intravenously) and halothane (0.5% to 1.5%) anesthesia, were performed in all sheep as previously described in detail [1]. Briefly, at the first sterile operation, flow probes (Transonic Inc, Ithaca, NY) were placed around the left main coronary artery and around the ascending aorta downstream from the coronary ostia through a left thoracotomy. A single hemispherical piezoelectric crystal was sutured to the base of the heart between the aorta and the main pulmonary artery, and the left hemiazygos vein was ligated.

At the second clean operation 1 to 2 weeks later, a median sternotomy incision was made, and one apical crystal and three pairs of sonomicrometry crystals (Sonotek Inc, Del Mar, CA) were placed on the left ventricle [1]. The crystals measured distances across three axes at right angles to each other. Wall thickness was measured by a fourth pair of crystals [1]. Micromanometer-tip pressure transducers (Millar Instruments, Inc, Houston, TX) were placed in the left ventricle, ascending aorta, and right atrium [1]. A flexible oxygen saturation catheter (Oximetrix Co, Mountain View, CA) was inserted into the coronary sinus. The surface electrocardiogram and inferior vena cava blood temperature were continuously monitored.

Changes in contractility were measured by insertion of a small occluder balloon (Datascope Inc, Oakland, NJ) in the ascending aorta downstream from the flow probe [2]. A custom intraaortic double-balloon catheter (Datascope) was inserted into the descending thoracic aorta just downstream from the left subclavian artery through the left femoral artery (Fig 1). The caudad occluder balloon had a volume of 12 mL; the cephalad balloon had a volume of 30 mL. When used, the occluder balloon was cyclically inflated for 15 seconds and released for 5 seconds using a custom-made control device that contains an electropneumatic inflator and a microprocessor timing system [2]. Two small-bore air cylinders (style B-12; Au-

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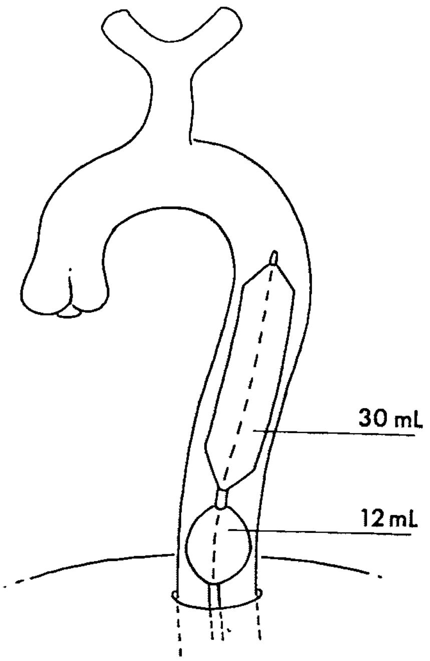

Fig 1. Custom intraaortic double-balloon catheter (Datascope).

rora Air Products) connected in series control inflation. The motion of the cylinders is regulated by a solenoid valve (Asco 8342), which is controlled precisely by a FORTH-based microcomputer board (New Micros) and a Rockwell R6512 microprocessor. The descending aortic catheter could be used in a single-balloon (occluder balloon deflated) or double-balloon mode (occluder balloon inflated): When inflated, the occluder balloon blocked blood flow in the descending thoracic aorta.

After the administration of heparin sodium (15,000 units intravenously), the animal was cannulated for cardiopulmonary bypass using a membrane oxygenator centrifugal pump system as previously described [1]. The arterial cannula (16F) was inserted into the right femoral artery. Cardiopulmonary bypass was started at 37°C. The left ventricle was decompressed through the apex; the aorta was clamped for 23 ± 2.6 minutes to produce global myocardial ischemia [1]. After the aortic clamp was released, the heart was reperfused, electrically defibrillated, and resuscitated for 76.2 ± 21.5 minutes (range, 54 to 113 minutes) using epinephrine (0.35 μg/kg/min) and lidocaine hydrochloride (1 mg/min). Bypass was stopped 34 ± 8.1 minutes (range, 30 to 52 minutes) after release of the aortic clamp. After ischemia, end-systolic elastance (Ees) decreased from 6.89 mm Hg/mL to 4.96 mm Hg/mL. All drugs were stopped at least ten minutes before metabolic and hemodynamic studies.

Four different configurations of mechanical circulatory assistance were studied.

1. Extracorporeal membrane oxygenation (ECMO). Blood was pumped at 35 mL/kg/min from the right atrium to the right femoral artery.
2. Intraaortic balloon counterpulsation (IABP). The descending thoracic aortic cephalad (30-mL) balloon was inflated at the beginning of diastole and deflated at the beginning of systole as timed from the surface electrocardiogram.
3. Extracorporeal membrane oxygenation plus IABP. The two methods just described were used simultaneously.
4. Extracorporeal membrane oxygenation plus the intraaortic double-balloon pump. Intraaortic balloon counterpulsation was used as described already with the second (12-mL) occluder balloon cyclically inflated for 15 seconds and deflated for 5 seconds during ECMO at 35 mL/kg/min.

The order of mechanically assisted interventions was determined by computer-generated randomization.

Measurements during control periods, which lasted at least 90 seconds, were made immediately before and immediately after each assist intervention, which lasted 90 to 120 seconds. If preintervention and postintervention control measurements of right atrial pressure, peak left ventricular pressure, or end-diastolic pressure differed by more than 10%, data were discarded and the study was repeated. Simultaneous hemodynamic and oxygen consumption measurements were made during the last 20 seconds of control and experimental periods after steady-state conditions were obtained. Previous work has shown no significant changes in left ventricular hemodynamics and oxygen consumption after 90 seconds of equilibration [1]. During the final 10 seconds of data acquisition, the impedance balloon in the aortic root was inflated to determine maximal Ees [2]. Thus left ventricular oxygen consumption and left ventricular pressure and volume were measured continuously for 10 seconds, and an index of left ventricular contractility, or Ees, was obtained immediately afterward. After completion of the entire protocol (four assist interventions and five control periods) one to three times, the animal was exsanguinated and the heart was excised, processed, and weighed as described previously [1].

During each 20-second data collection period, four left ventricular dimension signals, left ventricular pressure, right atrial pressure, aortic pressure, aortic and left main coronary flow, electrocardiogram, and coronary sinus blood oxygen saturation were simultaneously recorded on a 16-channel analog electrostatic strip-chart recorder (Gould ES-1000B). Data were digitally sampled with a 12-bit, 16-channel analog-digital convertor (Tecmar Lab Master, Solon, OH) in a Sperry PC/IT computer. All signals were sampled at 100 Hz and later digitally filtered with a 50-Hz low-pass filter. Arterial oxygen saturation was maintained at 100%; arterial oxygen tension, arterial carbon dioxide tension, and pH were measured (model 168; Corning Medical Inc, Corning, NY) every 30 to 60 minutes. Ultrasonic transit-time left main coronary artery blood flow measurements have been previously validated [1].

Changes in heart rate were controlled by programming the computer to reject all data points with cardiac cycle lengths 10% longer than or shorter than the mean cycle length of the previous 20-second control data collection period. To eliminate small variations between beats, five consecutive beats from each data set were selected at the point of end-expiration and then the signals were averaged.

Left ventricular pressure–volume loops were constructed from measured dimensions and recorded left ventricular pressures. A generalized ellipsoid model was assumed for calculation of left ventricular volume [3, 4]. Wall thickness was estimated from a continuous measurement of anterior wall thickness and postmortem measurements of septal, free wall, base, apical, anterior, and posterior wall dimensions. Dynamic endocardial volume was calculated by subtracting ventricular wall dimensions from epicardial values. Left ventricular volume measurements from sonomicrometry data have been previously validated [3].

The integrals of equatorial circumferential and meridional wall stress throughout systole or SSI were calculated using the equation of Falsetti and colleagues [5] and the equations of Sandler and Dodge [6]. The first derivative of left ventricular pressure was calculated for each beat. End-diastole was defined as that point on the upstroke of the first derivative of left ventricular pressure equal to 25% of the maximum [7]. End-systole was defined as the point of zero aortic flow.

End-systolic elastance, a measure of myocardial contractility [8], was determined from four single-beat volume–pressure loops using an aortic root impedance balloon [2]. The Ees was generated from the E_{max} (the point of maximum pressure divided by volume) of each loop using a shooting-point numerical iterative method [2, 9].

Left ventricular oxygen consumption was calculated from left main coronary artery blood flow because the ovine left coronary artery almost exclusively supplies the left ventricle [10]. Arteriovenous oxygen saturation differences were obtained from intermittent measurements of arterial oxygen tension and continuous measurements of coronary sinus blood oxygen saturation. Hemoglobin was measured periodically; the ovine binding coefficient is 1.35 [11].

The mean value of the control measurements before and after each assist intervention were compared with measurements during the assist intervention. The difference for each assist intervention was calculated, and significance was determined by Student's *t* test.

Results

The results of 17 comparisons between the four methods of mechanical assistance appear in Table 1. Although the intraaortic balloon significantly reduced the duration of systole, the decrease was small (5%); the other interventions did not significantly alter the duration of systole.

Extracorporeal membrane oxygenation at 35 mL/kg/min slightly increased left ventricular peak pressure (Fig 2A) and significantly reduced both end-diastolic volume and pressure (see Table 1). Systolic wall stress increased, as shown previously [3], although not significantly in these studies. The significant decrease in left ventricular oxygen consumption is not explained, as wall stress increased rather than decreased.

As expected, the intraaortic balloon significantly reduced left ventricular end-systolic pressure and volume (ie, afterload) (Fig 2B). It also slightly, but significantly, reduced end-diastolic pressure and volume (preload), and the SSI. Counterpulsation increased coronary artery blood flow. Despite significant reductions in left ventricular wall stress, we did not observe significant changes in left ventricular oxygen consumption.

The combination of ECMO and IABP significantly reduced end-diastolic volume (Fig 2C) and reduced systolic wall stress. Although coronary artery blood flow increased 18%, left ventricular oxygen consumption decreased.

When the descending thoracic aortic occluder balloon was inflated, ECMO perfused the lower body, and the effects of IABP were confined to the upper body. We expected a more significant decrease in left ventricular end-systolic pressure and volume, but the changes were less than those produced by IABP alone or in combination with ECMO (Fig 2D). The other changes were similar to and not significantly different from the combination of ECMO and IABP without the occluder balloon.

End-systolic elastance is a regression slope drawn between the end-systolic points of ventricular pressure–volume loops and is a measure of myocardial contractility [8, 12]. The Ees decreases after global ischemia, but the magnitude of the decrease varies widely between sheep [1]. This variation negates the value of mean data; therefore we calculated the difference between Ees during the assist intervention and the mean Ees of the preintervention and postintervention controls. With the exception of ECMO alone, IABP and the combinations of ECMO and IABP or the double-balloon pump increased the slope of Ees by similar magnitudes (Table 2).

Comment

Mechanical assist systems are not prescribed for normal hearts but for damaged, poorly contracting ventricles that are unable to sustain an adequate circulation. In sheep, warm ischemia for 25 minutes reduces myocardial contractility and moves ventricular pressure–volume loops to the right on the pressure–volume diagram [1, 3]. This model simulates the clinical problem of temporary cardiac dysfunction due to reversible causes. Without transplantation, survival requires that the native heart recover; therefore, the effect of various mechanical assist systems on ventricular volumes, wall stress, and oxygen consumption is highly relevant to recovery of myocardial contractility.

At this time, no one knows the mechanical and metabolic conditions that favor recovery of myocardial contractility after reversible ischemic injury [13, 14]. Oxygen consumption of stunned myocardium is greatly increased per unit of systolic wall stress compared with that of nonischemic myocardium [1]; ischemia decreases the efficiency of oxygen utilization [15]. Therefore, the postischemic heart is vulnerable to further ischemic injury, particularly if coronary arteries are diseased. Almost nothing is known of the mechanical conditions that favor recovery. Should the ventricle continue to eject? Do reductions in afterload or ventricular volumes or systolic wall stresses or any combination of these hasten recovery?

Table 1. Changes in Ventricular Mechanics and Oxygen Consumption[a]

Variable	Systolic Cycle Length (ms)	LV Peak Pressure (mm Hg)	LV End-Systolic Volume (mL)	LV End-Diastolic Pressure (mm Hg)	LV End-Diastolic Volume (mL)	Circumferential SSI (mm Hg · s)	Meridional SSI (mm Hg · s)	Coronary Artery Blood Flow (mL/min)	LV Oxygen Consumption (μL/100 g/beat)
Control	267.6 ± 75.6	57.9 ± 9.7	29.66 ± 10.44	6.7 ± 1.8	38.94 ± 11.9	11.4 ± 0.8	4.57 ± 1.68	101.7 ± 27.6	80.1 ± 8.9
ECMO	274.1 ± 63.9	59.5 ± 9.3	29.63 ± 12.3	6.0 ± 1.6	36.91 ± 13.3	12.1 ± 0.5	4.86 ± 2.12	107.9 ± 20.7	72.9 ± 9.0
Difference	+6.5 ± 16.9	+1.7 ± 6.2	−0.03 ± 3.11	−0.8 ± 1.2	−2.02 ± 3.76	+0.7 ± 2.4	+0.29 ± 1.06	+6.2 ± 18.2	−7.2 ± 8.5
p value (n = 17)	0.13	0.29	0.97	0.014[b]	0.04[b]	0.22	0.28	0.18	0.003[b]
Control	275.9 ± 73.4	57.3 ± 10.8	29.14 ± 10.3	6.8 ± 1.9	38.99 ± 12.0	11.6 ± 3.1	4.60 ± 1.61	105.4 ± 26.7	82.9 ± 41.4
IABP	261.2 ± 66.7	52.4 ± 12.4	27.84 ± 10.1	6.3 ± 1.9	37.61 ± 12.1	9.7 ± 2.5	3.80 ± 1.27	116.2 ± 36.6	84.6 ± 36.1
Difference	−14.6 ± 23.2	−4.8 ± 3.8	−1.3 ± 1.5	−0.5 ± 0.4	−1.38 ± 1.79	−1.9 ± 1.4	−0.81 ± 0.63	+11.2 ± 18.5	+1.7 ± 10.9
p value (n = 17)	0.02[b]	0.001[b]	0.003[b]	0.001[b]	0.005[b]	0.001[b]	0.001[b]	0.023[b]	0.52
Control	258.1 ± 65.2	56.4 ± 9.1	28.53 ± 9.9	6.6 ± 2.0	37.59 ± 10.5	10.8 ± 3.3	4.28 ± 1.64	99.5 ± 25.1	80.9 ± 37.4
ECMO + IABP	246.8 ± 56.1	54.3 ± 12.2	27.52 ± 11.1	5.7 ± 2.1	34.67 ± 10.8	9.9 ± 3.1	3.85 ± 1.57	117.3 ± 31.6	73.6 ± 36.0
Difference	−11.2 ± 44.4	−2.0 ± 7.6	−1.0 ± 2.3	−1.0 ± 0.8	−2.9 ± 2.4	−0.9 ± 2.4	−0.42 ± 1.04	+17.8 ± 23.1	−7.3 ± 13.1
p value (n = 16)	0.33	0.31	0.11	0.001[b]	0.001[b]	0.14	0.12	0.007[b]	0.041[b]
Control	264.4 ± 76.4	55.2 ± 9.4	28.49 ± 9.75	6.3 ± 2.0	37.38 ± 11.2	10.6 ± 3.6	4.18 ± 1.77	94.5 ± 25.7	78.1 ± 33.7
ECMO + DBP	258.9 ± 59.3	52.3 ± 11.7	27.33 ± 10.5	5.7 ± 2.2	34.83 ± 11.5	10.0 ± 4.3	3.89 ± 2.05	109.8 ± 28.9	71.5 ± 32.9
Difference	−5.6 ± 34.8	−2.9 ± 7.8	−1.15 ± 2.79	−0.6 ± 0.8	−2.54 ± 3.3	−0.6 ± 3.0	−0.29 ± 1.36	+15.3 ± 18.0	−6.7 ± 13.5
p value (n = 18)	0.51	0.13	0.098	0.007[b]	0.005[b]	0.39	0.38	0.002[b]	0.052[b]

[a] Data are shown as the mean ± the standard deviation. [b] A *p* value of less than 0.05 was considered significant.

DBP = double-balloon pump; ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon counterpulsation; LV = left ventricular; SSI = systolic stress integral.

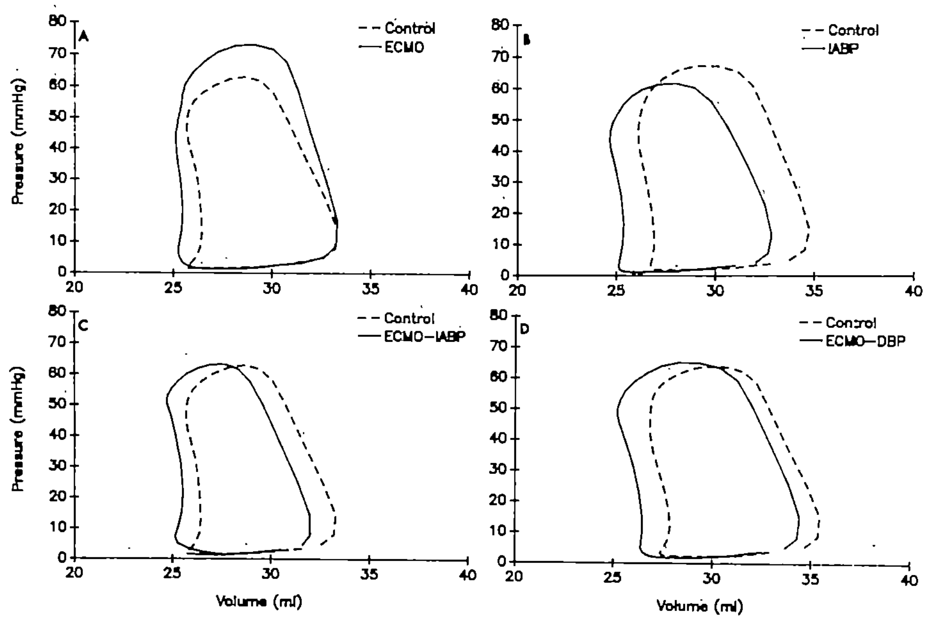

Fig 2. *Control and interventional left ventricular pressure-volume loops for each configuration of mechanical circulatory assistance from a single data collection protocol.* (ECMO = *extracorporeal membrane oxygenation at* 35 *mL/kg/min;* IABP = *intraaortic balloon pump;* DBP = *double-balloon pump.*)

This study was designed to determine the effect of four different mechanical circulatory assist systems on ventricular oxygen consumption and mechanics of the poorly contracting, dilated postischemic heart. The study does not define the conditions that favor recovery from ischemic injury, and does not include left ventricular assist devices or devices that completely substitute for cardiac function (ie, the native heart does not eject).

Extracorporeal membrane oxygenation and IABP have the important advantage that both systems can be quickly implemented with minimal or no surgical intervention from peripheral cannulation sites [16, 17]. Moreover, neither of the systems nor their combination requires a bedside technician to operate. As shown in our earlier study [3] and confirmed in this one, ECMO progressively increases left ventricular systolic wall stress of the postischemic heart but does not increase SSI of the normal heart. Extracorporeal membrane oxygenation alone increases left ventricular afterload and in the postischemic heart causes only a small decrease in left ventricular end-diastolic volume. Thus ECMO alone adds to the mechanical burden of the poorly contracting left ventricle, does not improve contractility, and seems unlikely to facilitate functional recovery of the myocardium.

Intraaortic balloon counterpulsation alone significantly reduces afterload and, somewhat surprisingly, preload. Systolic wall stress decreases, and coronary artery blood flow increases. Contractility improves. As documented by clinical experience, IABP facilitates recovery of myocardial contractility but does not circulate blood independently.

Combinations of ECMO and IABP have the advantages of reducing the increased afterload caused by ECMO alone with actual circulation of blood. With the combination of ECMO and IABP or the double-balloon pump, preload decreases significantly, and afterload and systolic wall stress also decrease. The improvement in contractility as measured by Ees is similar in magnitude to that associated with IABP alone. Small differences, variability, relatively few observations, and the nonrobustness of the Wilcoxon signed rank test may be relevant to the failure to reach significance (see Table 2).

The rationale of the occluder balloon was to augment the reduction in afterload produced by the balloon and to prevent the increase in afterload caused by ECMO alone. The occluder balloon in effect separates the body into upper and lower halves with independent arterial circulations. Extracorporeal membrane oxygenation perfuses the lower body, and the counterpulsated native heart perfuses the upper body. Periodic deflations of the occluder balloon prevent blood volume displacements. We

Table 2. Changes in End-Systolic Elastance[a]

Assist Type (Intervention)	Control	Intervention	Difference	p Value[b]
ECMO (n = 17)	5.31 ± 4.50	5.49 ± 4.22	+0.18 ± 1.09	>0.05
IABP (n = 17)	4.90 ± 3.31	6.13 ± 5.06	+1.23 ± 1.97	<0.01
ECMO + IABP (n = 16)	4.79 ± 2.84	5.88 ± 4.36	+1.08 ± 2.90	>0.05
ECMO + DBP (n = 18)	4.71 ± 2.84	5.68 ± 4.40	+0.97 ± 2.21	>0.05

[a] Data are shown as the mean ± the standard deviation. [b] Wilcoxon two-sample signed rank test for paired observations was used instead of Student's *t*-test for paired observations because the *F* tests for normal distributions were not satisfied.

DBP = double-balloon pump; ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon counterpulsation.

expected the reduced vascular bed of the upper body to augment the counterpulsating effect of the intraaortic balloon. The combination of the double-balloon pump and ECMO did not show any advantage over the ECMO-IABP system, but the data reinforced the rationale for using ECMO with balloon counterpulsation.

Some of the data on left ventricular oxygen consumption are discordant from data expected from changes in SSI. However, SSI is only one of several variables, including contractile state, that alters left ventricular oxygen consumption. Extracorporeal membrane oxygenation alone increased SSI, but decreased left ventricular oxygen consumption. Intraaortic balloon counterpulsation reduced SSI significantly but did not decrease left ventricular oxygen consumption. As recently observed, 25 minutes of warm ischemia markedly increases oxygen consumption and decreases oxygen utilization efficiency in sheep [15]. The magnitude of changes in consumption and utilization efficiency vary little within individual sheep but considerably between sheep. Ischemia also alters the partition between external or stroke work and elastic potential energy of the systolic pressure–volume diagram, which is a measure of total ventricular mechanical energy production [15]. Thus, although we believe our methods of measuring coronary blood flow and left ventricular oxygen consumption to be reasonably accurate, it is possible that the mechanical circulatory assist systems altered the efficiency of oxygen utilization in relation to SSI or the partition of total energy production in these postischemic hearts. We therefore are reluctant to derive conclusions from the data on left ventricular oxygen consumption until we have a better understanding of postischemic stunned myocardium.

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Bromocriptine as an Adjuvant to Cyclosporine Immunosuppression After Heart Transplantation

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Prolactin, a pituitary hormone, has been shown to have an active role in the regulation of the immune system. Prolactin receptors have been described on the membrane of lymphocyte cells, and competitive binding to these receptors by cyclosporine and circulating prolactin has been demonstrated. Experimental evidence suggests a synergistic effect of cyclosporine and bromocriptine, an inhibitor of pituitary release of prolactin, on immunosuppression. Between July 1986 and January 1988, 54 patients were randomly assigned to two groups of immunosuppression treatment. Thirty patients (group 1) were administered cyclosporine, azathioprine, and prednisone and 24 patients (group 2), a modified protocol aimed at decreasing the level of circulating prolactin by adding bromocriptine to the immunosuppression regimen. The two groups were similar in regard to age, preoperative diagnosis, and duration of follow-up. Minimal side effects related to bromocriptine were observed. The overall incidences of rejection and infection were similar, although actuarial analysis showed that freedom from these complications among patients treated with bromocriptine was significantly higher throughout the first 2 months after heart transplantation compared with that of patients in the control group. Other variables such as serum cyclosporine levels and lymphocyte counts were similar in both groups. In conclusion, suppression of circulating prolactin by bromocriptine appears to improve the immunosuppressive effect of cyclosporine, at least during the early postoperative period when the risk of rejection and infection is higher, and could be a promising avenue to successful hormonal manipulations of the immune process after organ transplantation.

(Ann Thorac Surg 1990;49:129–32)

Cardiac transplantation is now generally recognized as a valuable treatment of end-stage cardiac disease [1]. The excellent results obtained in recent years have been attributed to the use of better immunosuppression, particularly after cyclosporine was introduced [2]. However, because of the many toxic effects of the latter, alternative approaches need to be developed. The possibility of modulating the immune response through interactions between hormonal and immune systems is currently under investigation [3].

Prolactin, a pituitary hormone, has been shown to play an active role in the regulation of the immune system [3]. Prolactin receptors have been found on the membrane of lymphocyte cells, and it has been suggested that competitive binding of cyclosporine and circulating prolactin to these receptors may occur [4–6]. Experimental evidence suggests that hormonal manipulation of the immune system may be a promising approach to improve immunosuppression after organ transplantation [7].

Bromocriptine, an inhibitor of prolactin pituitary release, has been found to act synergistically with cyclosporine in animal models of autoimmune disease as well as in experimental transplantation [8, 9]. The effects of bromocriptine as an adjunct to cyclosporine immunosuppression after cardiac transplantation were evaluated in a prospective randomized study performed at the University of Arizona and at the Montreal Heart Institute. The aim of the present study was to determine the value of adding bromocriptine to the immunosuppression regimen to decrease the incidence of acute rejection and infection after human cardiac transplantation.

Material and Methods

Patient Population

From July 1986 to January 1988, 54 patients were randomly assigned by chart number to two groups of immunosuppression treatment. Group 1 included 30 patients who received conventional immunosuppression with cyclosporine, azathioprine, and prednisone. Twenty-four patients were assigned to group 2 with the following protocol: intravenous infusion of dopamine hydrochloride (1 µg/kg/min) for the first three to four days after transplantation and then oral administration of bromocriptine, 7.5 mg/day in three doses, along with cyclosporine, azathioprine, and prednisone. Bromocriptine was discontinued 6 months postoperatively.

In both groups, cyclosporine treatment was initiated preoperatively, and postoperative plasma levels were monitored regularly. Trough levels were maintained between 150 and 200 ng/mL during the first postoperative month and between 75 and 150 ng/mL thereafter. Cyclosporine levels were measured by radioimmunoassay. Azathioprine was given preoperatively at the dose of 4

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mg/kg, and postoperatively the daily dose was adjusted to maintain the white blood cell count between 5,000 and 10,000 cells/μL. In addition, all 41 patients operated on at the University of Arizona (23 patients of group 1 and 18 of group 2) were given rabbit antithymocyte globulin perioperatively for three days. In these patients, the incidence of rejection was similar to that of the remaining 13 patients (1 ± 0.8 versus 0.8 ± 0.8 episode/patient; not significant).

Plasma prolactin levels were determined daily during the hospitalization period after transplantation in 28 patients. Duplicate determinations of circulating prolactin were performed by the use of a double-antibody radioimmunoassay commercial kit. All samples from the same patient were run using the same assay kit.

Endomyocardial biopsy performed on a weekly basis was used to detect cardiac rejection, and for all patients of both institutions, the diagnosis of rejection was based on the criteria of acute rejection defined by Billingham [10]. In the present study, rejection or infection was defined as an episode requiring specific treatment with an increase in immunosuppression or with specific antimicrobial treatment, respectively.

Data Analysis

The complication-free rates of rejection and infection were analyzed by the actuarial method [11]. Student's *t* test and the χ^2 test were used for statistical analysis of the data. The level of statistical significance was established at the probability level of 95%. Actuarial curves for the entire follow-up period were compared using the Mantel-Cox test. As the risk of rejection decreases rapidly with time after transplantation and is maximal during the first 2 months, a secondary analysis of the first 2 postoperative months was performed using the Mantel-Cox test to compare curves and the χ^2 test to compare individual intervals [11]. Results are expressed as the mean ± the standard error of the mean.

Table 1. Summary of Patient Data

Variable	Group 1[a]	Group 2[a]
No. randomized	30	24
Age (yr)[b]	45 ± 2.5	47 ± 1.6
Sex		
Male	28	23
Female	2	1
Preoperative diagnosis		
Ischemic	19	16
Idiopathic	8	8
Congenital	3	0
Follow-up (mo)[b]	5.9 ± 0.1	5.6 ± 0.2

[a] Group 1 received cyclosporine, azathioprine, and prednisone, and group 2 received bromocriptine in addition to these three drugs.
[b] Data are shown as the mean ± the standard error of the mean.

Results

The groups were similar in regard to age, preoperative diagnosis, and duration of follow-up (Table 1). Bromocriptine had to be discontinued 1 month postoperatively in 1 patient because of dizziness. In another patient, bromocriptine was initiated 1 month after transplantation when severe acute rejection developed. These 2 patients were therefore included in their initial treatment group and were withdrawn from the study when their treatment was modified.

There were a total of 32 acute rejection episodes in group 1 (control group, no bromocriptine) and 23 in group 2 (treated with bromocriptine), for a respective incidence rate of 1 ± 0.1 and 0.9 ± 0.2 episode per patient. There were eight episodes of infection in group 1 and seven in group 2, resulting in an equal incidence of infection in both groups (0.3 ± 0.1 episode per patient).

The actuarial analysis of rejection episodes indicates that freedom from rejection among patients treated with bromocriptine was higher, but the difference between the two curves for the whole follow-up did not reach significance (Fig 1). In 1 patient, the first rejection episode developed more than 2 months postoperatively. The analysis of the initial 2-month period indicates a significantly higher freedom rate from rejection among bromocriptine-treated patients (Mantel-Cox: $p < 0.01$; χ^2 at 1 month and 2 months: $p < 0.05$). The analysis of infection-free rates indicates a higher freedom rate for patients treated with bromocriptine, but the difference did not reach the level of significance by Mantel-Cox analysis of the curves (Fig 2). However, the difference at the 2-month period was significant by χ^2 analysis ($p < 0.05$).

Both groups were similar in regard to plasma cyclosporine levels and total peripheral lymphocyte counts (Figs 3, 4). Serum creatinine levels and arterial blood pressure were also similar (Figs 5, 6). Circulating plasma prolactin levels were almost undetectable during the period of hospitalization in most patients in group 2 (Fig 7). However, during the same period, higher levels of circulating prolactin despite medication occurred in 4 patients treated

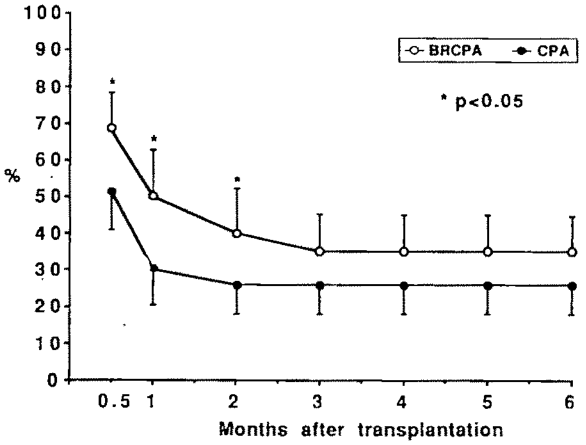

Fig 1. Actuarial freedom from rejection in group 1 (CPA [cyclosporine, prednisone, azathioprine]) (n = 30) and group 2 (BRCPA [bromocriptine, cyclosporine, prednisone, azathioprine]) (n = 24). Mantel-Cox analysis of the 6-month data = not significant; Mantel-Cox analysis of the first 2 months, $p < 0.01$; *χ^2 analysis of 0.5-month, 1-month, and 2-month proportions,* $p < 0.05$.

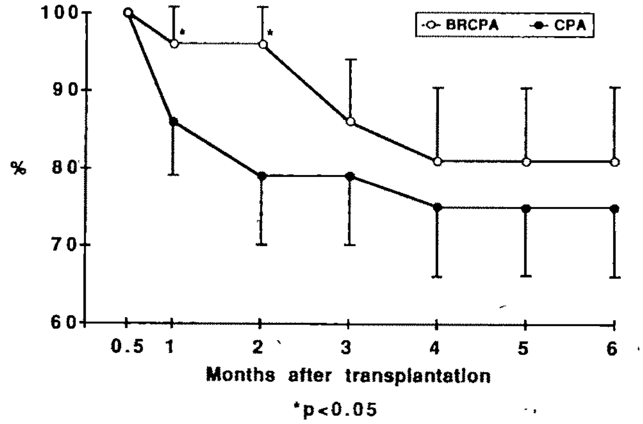

Fig 2. *Actuarial freedom from infection in group 1* (CPA) (n = 30) *and group 2* (BRCPA) *(n = 24). Mantel-Cox analysis of the 6-month data = not significant; χ^2 analysis of proportions at 2 months,* $p < 0.05$. *CPA and BRCPA are as in Figure 1 legend.*

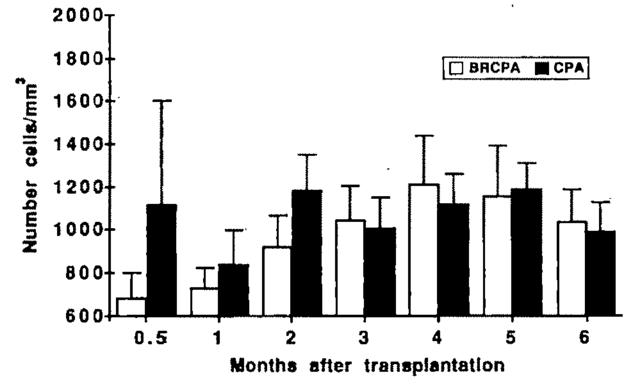

Fig 4. Total lymphocyte counts in group 1 (CPA) (n = 30) and group 2 (BRCPA) (n = 24). CPA and BRCPA are as in Figure 1 legend.

with bromocriptine, thus indicating that prolactin secretion was not completely suppressed in some patients with the doses of bromocriptine administered in this study.

Comment

Day-to-day changes in circulating prolactin levels after cardiac transplantation have been previously defined, and a sudden increase in prolactin has been shown to occur with acute allograft rejection [12, 13]. It has also been established, both in vitro and in experimental animal models, that prolactin plays an active role in the regulation of the immune system [3]. Hormonal manipulation of the immune response could therefore become a useful approach to immunosuppression in organ transplantation.

Bromocriptine has been shown to have a synergistic effect with cyclosporine to increase immunosuppression through inhibition of prolactin pituitary release in experimental transplantation and in animals with autoimmune disease [7–9]. The increased immunosuppressive effects of this association could result from a decrease in immunological stimulation, due to lower levels of serum prolactin or from an increase in cyclosporine binding to lymphocytes. In the present study, suppression of prolactin release during the early postoperative period was obtained by dopamine infusion, which is known to decrease pituitary excretion of prolactin [14]. Bromocriptine was administered from the third or fourth postoperative day throughout the initial 6-month period after transplantation [15, 16]. The early postoperative period is of particular interest because of the higher incidence of acute rejection during the first 2 to 3 months after heart transplantation. Thereafter, a state of immunological tolerance appears to be induced in patients treated with an immunosuppression regimen including cyclosporine, and the occurrence of infection decreases markedly [17].

Our study indicates a higher freedom rate from rejection and from major infection during the first 2 months after heart transplantation when bromocriptine is administered in association with conventional triple-immunosuppression therapy. In patients receiving bromocriptine, an effective suppression of circulating prolactin was shown. On the other hand, our two groups of patients

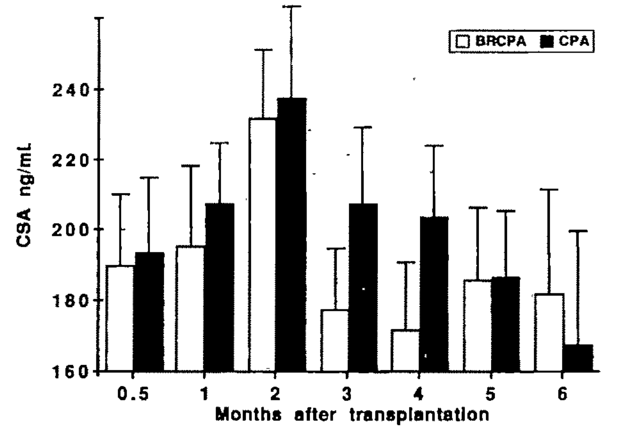

Fig 3. Cyclosporine (CSA) trough levels in group 1 (CPA) (n = 30) and group 2 (BRCPA) (n = 24). CPA and BRCPA are as in Figure 1 legend.

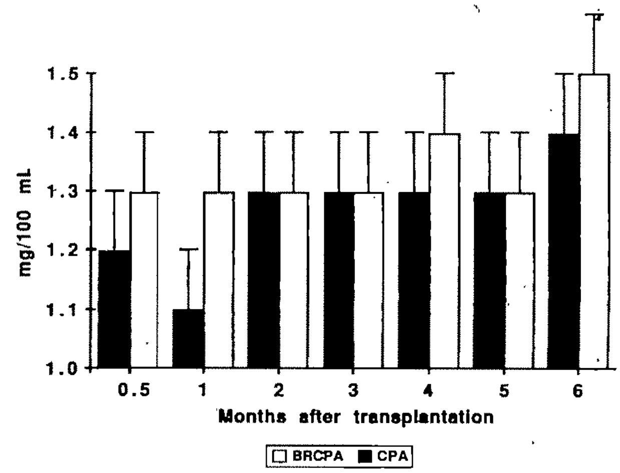

Fig 5. Serum creatinine levels in group 1 (CPA) (n = 30) and group 2 (BRCPA) (n = 24). CPA and BRCPA are as in Figure 1 legend.

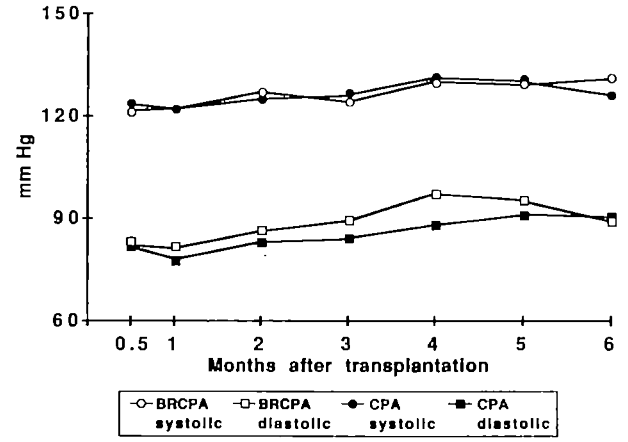

Fig 6. Systolic and diastolic blood pressures in group 1 (CPA) (n = 30) and group 2 (BRCPA) (n = 24). CPA and BRCPA are as in Figure 1 legend.

were similar in regard to other clinical and bioclinical variables; plasma cyclosporine and serum creatinine levels were similar, as were peripheral lymphocyte counts and systemic blood pressure. No major complications occurred after bromocriptine administration, and side effects were minimal. They consisted mainly of dizziness and nausea, which necessitated termination of treatment in only 1 patient.

A decrease in rejection rate was observed despite the fact that bromocriptine at the doses used in this study did not appear to suppress circulating prolactin levels completely in some of the patients.

Recent clinical reports indicate that a triple-drug regimen including cyclosporine, azathioprine, and prednisone results in better immunosuppression and fewer complications compared with the previous double-drug protocol of cyclosporine and prednisone [18]. Prolactin inhibition with bromocriptine may provide an additional benefit to the triple-drug therapy by improving the immunosuppressive effect of cyclosporine without increasing the side effects. However, before it is recommended as standard treatment, further confirmation in a larger group of patients is necessary to obviate the risk of a β error in a small randomized study.

In conclusion, suppression of circulating prolactin levels with bromocriptine appears to improve the immunosuppressive effect of cyclosporine, thereby resulting in a lower incidence of early acute rejection as well as infection after cardiac transplantation. Effective suppression of prolactin release by the use of bromocriptine or other drugs could prove to be a useful adjunct to immunosuppression through successful hormonal manipulation of the immune system after organ transplantation.

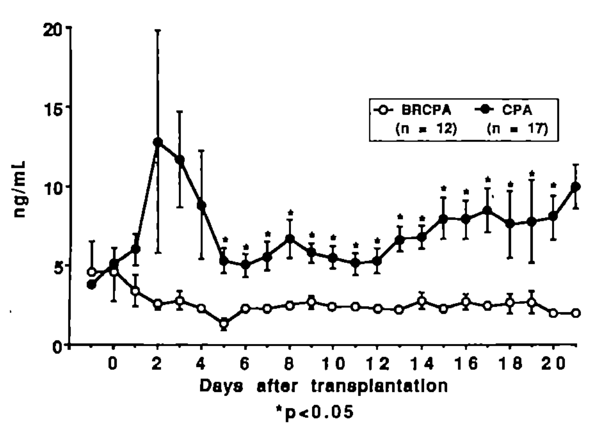

Fig 7. Plasma prolactin levels in group 1 (CPA) and group 2 (BRCPA). CPA and BRCPA are as in Figure 1 legend.

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Effect of Routine Fibrin Glue Use on the Duration of Air Leaks After Lobectomy

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The effectiveness of fibrin glue as a sealant to reduce postoperative air leaks after pulmonary lobectomy was evaluated in 28 consecutive patients between November 1988 and May 1989. A fibrin glue spray was used in 14 patients, and 14 patients served as controls. Assignment of either group was made before thoracotomy. Nine male and 5 female patients with a mean age of 63.8 years were in the fibrin glue experimental group, and 8 male and 6 female patients with a mean age of 59 years, in the control group. An equal number of complete and incomplete fissures were in each group. All fissures were handled in the same way (stapled). Two milliliters of fibrin glue was applied through a double-syringe delivery system and sprayed on the staple line and any cut surface of the inflated lung just before thoracotomy closure. The fibrin glue-treated group had a mean air leak duration of 2.3 ± 3.7 days, chest tube drains for 6 ± 4.1 days, and a postoperative hospitalization of 9.8 ± 3.1 days. The control group had a mean air leak duration of 3.3 ± 3.3 days ($p = 0.94$), chest tube drains for 5.9 ± 3.9 days ($p = 0.95$), and a postoperative hospitalization of 11.5 ± 3.9 days ($p = 0.21$). We conclude that the routine use of a fixed quantity of fibrin glue is not effective in reducing the duration of air leaks, chest tube drainage, or hospitalization after uncomplicated pulmonary lobectomy.

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Prolonged air leak after pulmonary lobectomy is a complication associated with increased morbidity and length of postoperative hospitalization [1]. In most instances the air leak will eventually close or the lung will become adherent to the chest wall preventing collapse if the chest tube is removed.

Fibrin glue has been shown experimentally in animals to be an effective sealant for pulmonary parenchymal defects [2–4]. Clinical experience in 10 patients undergoing lobectomy showed a significant increase in pressure tolerance after application of fibrin glue to conventional sutures when tested intraoperatively [2].

The purpose of the present study was to determine whether the routine use of a standard quantity of fibrin glue would influence the duration of postoperative air leaks after uncomplicated lobectomy.

Material and Methods

Twenty-eight consecutive patients requiring uncomplicated lobectomy between November 1988 and May 1989 were the subject of this study. Fast-acting Tisseel (Immuno AG, Vienna, Austria), a commercially available kit of two-component fibrin glue, was used. The fibrin sealant is formed by mixing the sealer solution (fibrinogen, factor XIII, fibronectin, aprotinin, and plasminogen) with the thrombin solution (thrombin and calcium chloride). This was prepared according to the manufacturer's specifications.

Before thoracotomy each patient was assigned to the fibrin glue experimental group or the control group in a randomized fashion based on the patient's admission number. There were 14 patients in each group. All fissures were handled in the same manner and were divided with linear stapling devices (Ethicon Company, Peterborough, Ontario, Canada). The average cost of stapling the fissure was $163.00. The remaining lung was fully inflated after completion of the procedure. Two milliliters of fibrin glue was then applied through a double-syringe spray delivery system to the staple line and to any cut surface of the lung regardless of the presence or absence of an air leak. The cost of the fibrin glue application was $170.00. Postoperative care was the same in both groups. The duration of postoperative air leaks, chest tube drainage, and postoperative hospitalization was recorded. Statistical analysis was performed using Student's t test.

Results

The fibrin glue group consisted of 9 male and 5 female patients with a mean age of 63.8 years, and the control group consisted of 8 male and 6 female patients with a mean age of 59.0 years. The diagnoses and lobes resected are listed in Table 1. All patients in the control group and 13 patients in the fibrin glue group had a positive smoking history. The status of the fissures was the same in both groups. Ten patients had incomplete fissures, and 4 patients, complete fissures. Three patients in each group had no air leak at the termination of the procedure. There was no significant difference in the duration of postoperative air leaks ($p = 0.94$) or the number of days the chest

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Table 1. Diagnosis and Lobectomy Specimens

Variable	Fibrin Glue (n)	Control (n)
Diagnosis		
Bronchogenic carcinoma	10	10
Metastatic carcinoma	2	. . .
Benign	1	3
Primary lymphoma	1	. . .
Atypical carcinoid	. . .	1
Lobe resected		
Right upper	8	6
Right lower	2	4
Left upper	2	1
Left lower	2	3

tubes were required ($p = 0.95$) in the fibrin glue or the control groups. The duration of postoperative hospitalization was essentially the same for both groups ($p = 0.21$) (Table 2).

Air leaks greater than seven days duration occurred in 2 patients in the fibrin glue group (eight and 14 days) and one patient in the control group (12 days). Other postoperative complications included atrial fibrillation (1 fibrin glue, 3 control), pleural effusion (1 control), dehydration (1 fibrin glue), pneumonia (1 control), and urinary tract infection (1 control). There were no complications related to the fibrin glue.

Comment

Fibrin glue is a biological tissue adhesive that mimics the last step of the blood clotting cascade. The mechanism of action and its application have been well described [5]. Briefly, when the sealer and thrombin solution are mixed, fibrinogen is converted to fibrin by thrombin, clotting is initiated, and the mixture becomes solid. In the presence of ionized calcium, thrombin also activates factor XIII to factor XIIIa, which catalyzes the cross linkage of fibrin and results in increasing the strength of the clots. Aprotinin is an antiproteolytic enzyme that is added to inhibit degradation. There is also evidence that fibrin stimulates the growth of fibroblasts and enhances wound healing [3, 5]. Experimentally, fibrin glue has been shown to reduce pulmonary air leaks [2–4]. Bergsland and associates [3] have shown that fibrin glue rapidly gains strength by demonstrating in rabbits that the pressure required to produce air leaks in fibrin glue-repaired pulmonary defects was greater on day 14 than on day 1.

Table 2. Results of the Standard Application of Fibrin Glue

Group	n	Air Leak (days)[a]	Chest Tube Drainage (days)[a]	Hospitalization (days)[a]
Staple and fibrin glue	14	3.2 ± 3.7[b]	6.0 ± 4.1[c]	9.8 ± 3.1[d]
Staple (control)	14	3.3 ± 3.3	5.9 ± 3.9	11.5 ± 3.9

[a] Values are given as mean ± standard deviation. [b] t value versus control = −0.08. [c] t value versus control = 0.07. [d] t value versus control = −1.3.

Clinical experience with fibrin glue for reducing pulmonary air leaks has been sparse, and the vast majority of experience comes from Europe. Türk and co-workers [2] demonstrated a 36% increase in pressure tolerance in 10 patients after application of fibrin glue to conventional sutures when measured intraoperatively. They recommended fibrin adhesive be applied to pulmonary suture lines as a proper technique for reducing air leaks. However, the use of staples for the division of fissures is considered superior to conventional suturing [6]. Other reports of clinical use of fibrin glue use are single cases [7] or bronchoscopic application for closure of various fistulas [8], in which no conclusive statements can be made.

In this series, all the fissures were stapled. The application of the sealant consisted of a double-syringe delivery system that assured mixing of the two components and a spray of compressed air that evenly distributed a thin film of glue over the lung. The purpose of this study was to determine whether the routine use of a fixed quantity of fibrin glue would be beneficial. When used in this fashion fibrin glue had no effect in reducing the duration of air leaks, chest tube drainage, or hospitalization. Intraoperative air leaks were not measured before or after application of the glue. It is possible that the application of additional sealant until no intraoperative air leak could be demonstrated may be effective; however, this cannot be answered from the present study.

In conclusion, the routine use of fibrin glue cannot be recommended to reduce pulmonary air leaks after lobectomy. Meticulous dissection and stapling of fissures remains an important technique in reducing this complication. The selective use of fibrin glue after pulmonary resection merits further clinical investigation.

We are grateful to Eva Germann, MSc, for providing the statistical analysis.

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Sternal Wire-Induced Persistent Chest Pain: A Possible Hypersensitivity Reaction

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Persistent chest pain has been reported to be a relatively common complaint after operations through a median sternotomy approach. We report a case that we believe represents a sternal pain syndrome resulting from sensitivity to nickel in the stainless steel sternal wires. In view of the high incidence of nickel sensitivity in the general population, we question whether such sensitivity may be involved in similar poststernotomy pain syndromes when any other clear-cut pathophysiological process is not apparent.

(Ann Thorac Surg 1990;49:135–6)

Persistent sternal pain after median sternotomy for open heart operations is reported as a relatively common complaint. Many poststernotomy pain syndromes have been defined with a specific cause–effect relationship directly related to an underlying pathological process (eg, infection, nonunion, protruding wire, ischemia) [1]. Most cases appear to be poorly defined, however, and have been attributed to nonspecific anxiety-related or muscular pain disorders. We report a case of disabling chest pain after an open heart operation through a median sternotomy incision in which stainless steel sutures were used for sternal closure. Removal of the sternal wires led to complete relief of pain.

A 47-year-old woman underwent ablative therapy through a midline sternotomy incision for treatment of Wolff-Parkinson-White syndrome. This procedure was successful, but the patient had persistent periincisional pain that increased with motion and was unable to return to work 2 months postoperatively. Computed tomography of the chest revealed a partial nonunion of the lower aspect of the anterior table of the sternum, although there was no clinically apparent instability. Because of the patient's continuing pain, we decided to split and rewire the sternum surgically, with the hope of alleviating her pain.

About five days postoperatively, the patient again began to experience disabling pain beneath the skin incision such that she was unable to return to work or perform most household duties; she continued to require analgesic medication. She was referred to our pain clinic 2 months after this repair with radiographic evidence of a solid sternal fusion and no broken or protruding wires. Her pain had been unresponsive to nonsteroidal antiinflammatory drugs, nortriptyline, and clonazepam.

Physical examination showed a well-healed midsternal scar. There was no evidence of trigger-point tenderness or clinical signs of infection. There was tenderness to palpation of the periincisional area throughout that reproduced her pain symptoms. A trial of topical capsaicin cream (Zostrix; GenDerm Corp, Northbrook, IL) was discontinued when the patient reported a severe rash after the first dose.

Due to the severity of this rash, we sought a more detailed history, which revealed multiple allergic reactions in the past, including skin sensitivity to jewelry. The stainless steel sutures used to close the patient's sternum in both operations contained 8% nickel (Ethicon). Because skin patch-testing showed that the patient was 4+ reactive to nickel, she consented to surgical removal of the wires.

Examination of the sternum at the time of operation revealed that all wires were intact and the sternum was well healed. All wire sutures were removed. The patient was discharged from the hospital later that day with a complaint of mild incisional pain. This resolved in a few days, and she returned to full-time employment without pain and required no analgesic medication. She continued to be asymptomatic at 3-month follow-up.

Comment

We found only 1 other case in the literature in which removal of intact, nonprotruding wire sutures resolved disabling sternal pain [2]. That patient's reaction to the sutures was not explained, however. We hypothesize that sensitivity to the nickel component in the stainless steel sutures can account for our patient's symptoms. This hypothesis is based on the indirect evidence of this woman's 4+ patch test reactivity and her history of previous skin hypersensitivity reactions. We recognize, with hindsight, that a tissue biopsy at the time of suture removal could have yielded conclusive evidence. A tissue reaction compatible with allergy would have supported this hypothesis.

Without this evidence, but in the face of completely intact, well-placed sutures, with no soft tissue protrusion and a solidly fused sternum, the complete resolution of

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this patient's pain several days after removal of the sutures is highly suggestive that a nonmechanical type of reaction was operative.

Allergic reactions to skin clips have been reported, with the determination that these reactions are caused by the nickel content in surgical grade stainless steel clips [3]. It has been suggested that a history of metal sensitivity should be sought in patients undergoing surgical procedures in which skin clips might be used for wound closure. A recent large multicenter epidemiological study demonstrated an overall incidence of nickel hypersensitivity of 7.3%. Nickel hypersensitivity is more common in females (10.5%) than in males (2.1%) [4]. Because of this 5:1 ratio of females to males demonstrating nickel hypersensitivity, it would be interesting to know the prevalence of females who have poststernal wiring pain as compared with males. We are unaware of any studies reporting such data. Although some prospective studies have addressed the long-term tissue reactivity to some synthetic sutures, stainless steel (which incorporates nickel) has not been included [5]. The importance of considering potentially treatable causes of postoperative sternal pain before attributing such symptoms to anxiety or incisional pain has been stressed [1]. We question whether the common occurrence of nickel sensitivity in the general population might contribute to persistent poststernotomy pain when stainless steel sutures are used for closure. If so, this pain syndrome is both curable and preventable by the selection of other suture material.

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Obstructing Tracheal Lipoma: Management of a Rare Tumor

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Benign neoplasms of the trachea are rare. We describe a 46-year-old patient with a lipoma arising from the membranous trachea and causing severe respiratory obstruction. Investigation and management of this problem are discussed, and the literature is reviewed.

(Ann Thorac Surg 1990;49:137–9)

Only a few large series of primary tracheal tumors have been reported, and most of these lesions have been malignant. The incidence of benign tumors reported ranges from 4.5% to 33% [1–3], and tracheal lipomas are among the rarest.

A 46-year-old man was evaluated for a 10-month history of wheezing and a tight feeling in his chest. He had stopped smoking 3 months before his referral. He had inspiratory stridor and bilateral basal wheezes; chest roentgenogram showed left basal consolidation. The ratio of forced expiratory volume in 1 second to forced vital capacity was 3.3/4.65, and spirometry trace indicated obstruction of the large airways (Fig 1) with a peak expiratory flow rate of only 265 L/min.

Tracheal tomograms showed a polypoid mass approximately 2 cm in diameter in the trachea at the thoracic outlet (Fig 2). Fiberoptic bronchoscopy showed a fleshy mass almost completely occluding the trachea, but a biopsy was not performed because of the risk of severe hemorrhage. A computed tomographic scan showed the mass to arise from the membranous part of the trachea and apparently spread outside the trachea (Fig 3). The possibility of a benign lipoma was considered because of the low attenuation numbers of the lesion, but this was thought to be unlikely because of the apparent spread outside the trachea. The patient was referred for urgent operation because of severe respiratory obstruction.

A preliminary rigid bronchoscopy at operation confirmed a fleshy, wide-based mass arising 4 cm below the vocal cords and nearly occluding the lumen. However, the bronchoscope could be passed beyond the tumor. A small bougie was left in place beyond the tumor on removal of the bronchoscope to aid endotracheal intubation. Because the diagnosis of the tumor was in doubt, we decided to perform a formal tracheal resection.

With the patient's neck extended, a collar incision was made. The tracheal ring immediately below the tumor was identified from the computed tomographic scan, and the trachea was transected below this ring. The endotracheal tube was withdrawn until just proximal to the tumor, and a second tube was passed into the distal end of the transected trachea (Fig 4). The tumor was easily separated from the esophagus, and 4.5-cm length of trachea including the tumor was resected. Clear resection margins were confirmed by frozen section. End-to-end anastomosis of the trachea was achieved with interrupted absorbable (Vicryl) sutures. Tension across the anastomosis was minimized by suturing the chin to the chest; sutures were removed on the seventh postoperative day. The patient made an uneventful postoperative recovery and was discharged on the 13th postoperative day. Histological examination of the tumor showed it to be a benign pure lipoma (Fig 5).

Comment

Benign tracheal tumors are rare. Only 5 cases of tracheal lipomas have been previously reported in the world literature. Three were mentioned as part of large series [3–5] and 2 were independently described [6, 7], but only 1 was composed purely of adult adipose tissue [7]. The

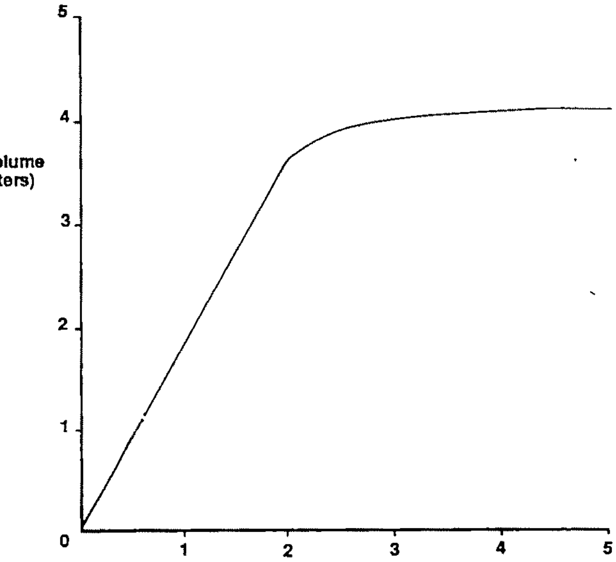

Fig 1. Spirometry trace shows linear relationship between volume and time and a reduced maximum flow rate during most of expiration.

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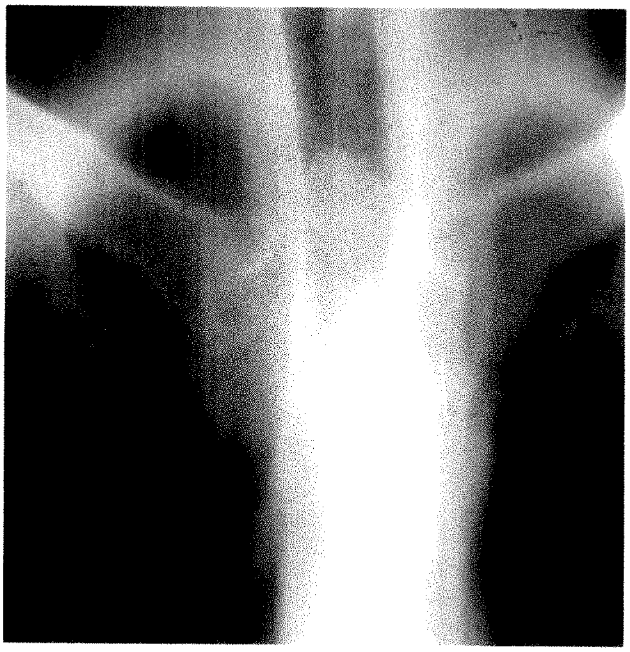


Fig 2. A cut of the tracheal tomogram shows a polypoid mass completely filling the lumen of the trachea at the level of the thoracic inlet.

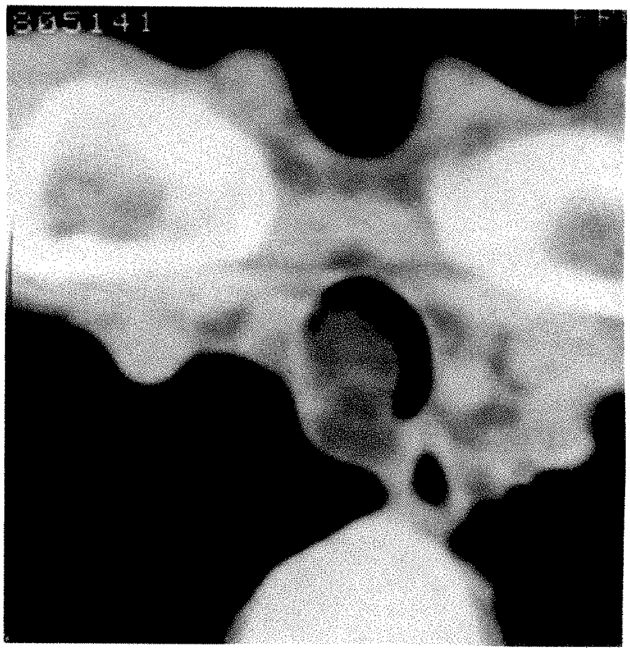


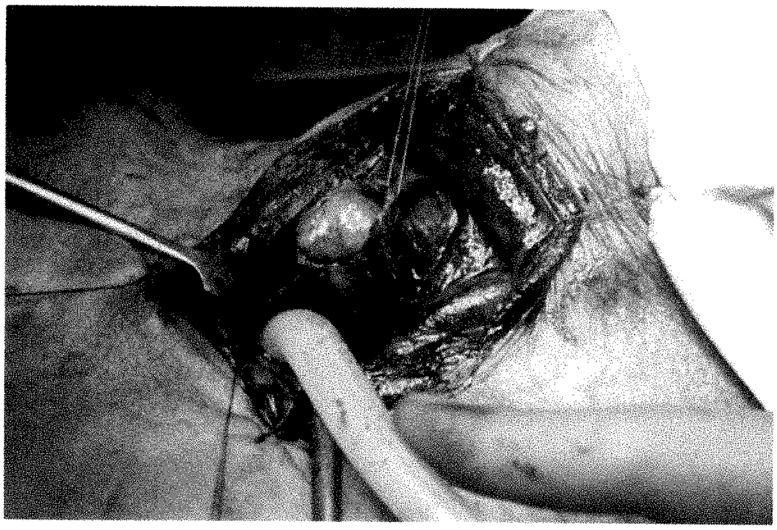
Fig 3. Computed tomographic scan at a level similar to that shown in Figure 2 shows the lesion almost filling the tracheal lumen with apparent posterior extension into the surrounding tissues.

pathogenesis of these lipomas is unclear; they may arise from fully differentiated lipocytes or primitive mesenchymal cells. Most of the adipose tissue in the major airways lies outside cartilage, but small amounts are present in the submucosa [5]. In mixed tumors, glandular tissue may become incorporated during tissue proliferation and other mesodermal elements may arise by separate differentiation from primitive mesenchymal cells.

Our patient had the classic symptoms of an obstructing lesion in the trachea: cough, wheeze, dyspnea, and stridor—the "tracheal syndrome." This syndrome is present in up to 85% of patients with primary tracheal tumors, but such patients are often misdiagnosed as asthmatics and treated as such for protracted periods before the correct diagnosis is made. The mean interval between onset of the first symptoms and diagnosis is 25 months in benign lesions and 8 months in malignant lesions [4].

In our patient, the diagnosis was suspected at the first consultation and tomograms of the trachea confirmed these suspicions. Although less commonly performed since the advent of computed tomographic scanning, tracheal tomography is useful as it allows a longitudinal view of the lesion. Very high quality longitudinal scans may now be achieved with magnetic resonance imaging, but this is not commonly available. Overpenetrated chest roentgenograms and xeroradiography have also been

Fig 4. The trachea was transected and the proximal end, with the lipoma protruding from it, was elevated to allow insertion of a sterile endotracheal tube into the distal lumen.



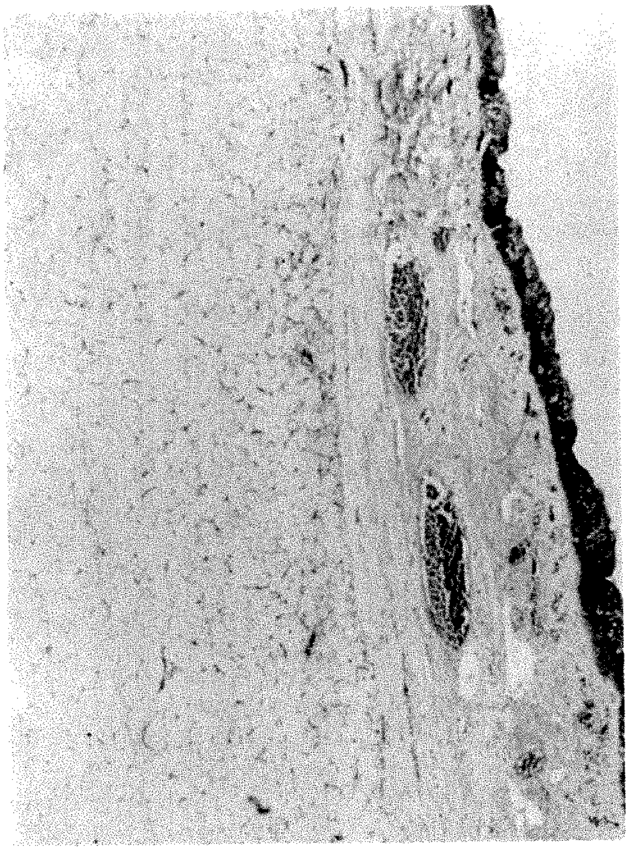


Fig 5. Resected tumor. The covering respiratory epithelium and its homogenous nature is evident. (Hematoxylin and eosin, ×80 before 22% reduction.)

recommended as other useful initial investigations [4]. Computed tomographic scanning is valuable in localizing the origin and extent of the tumor, assessing its spread, and detecting localized lymph node enlargement. In this case, the low attenuation numbers of the tumor on the computed tomographic scan suggested its nature but also suggested local invasion. An obstructive lesion in the trachea is indicated by the linear relationship between volume and time on spirometry, a flat-topped expiratory flow-volume loop, and a low peak flow rate relative to the forced expiratory volume in 1 second.

The need for preoperative diagnosis is controversial. Perelman and associates [3] believe that biopsy should be performed as a separate procedure before the planned surgical treatment. Eschapasse [1] reported that biopsy may be traumatic and potentially hazardous, with risk of hemorrhage leading to complete tracheal obstruction, and should only be performed with full surgical facilities available. Grillo [8] stated that in radiologically well-defined tumors that appear to be completely resectable biopsy can be deferred until the planned surgical procedure but should be performed as a preliminary procedure if the tumor appears to be extensive.

Lipomas confined to the lumen of the trachea may be removed endoscopically, and recurrence has not been reported. For the few lipomas seen to be penetrating through the spaces between cartilage, larger resections were performed to ensure complete removal and prevent recurrence.

In our patient, resection of the tumor was performed because the tumor had a wide base and appeared to extend beyond the membranous wall of the trachea, which it almost totally occluded. Meticulous technique should make the mortality and morbidity of tracheal resection low. Use of absorbable sutures in the tracheal anastomosis, with specific care taken to avoid unnecessary tracheal devascularization, and reduction in anastomotic tension by flexion of the neck postoperatively are important points to be observed.

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Survival After Embolization of a Complete Prosthetic Aortic Valve to the Aortic Arch

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Partial dehiscence and embolization of poppets, leaflets, and discs are well-known complications of mechanical valve prostheses. Dehiscence with embolization of an entire prosthetic valve is rare. Previous reports of dehiscence and embolization of an entire prosthetic valve are associated with fatality and are the subject of autopsy reports. We report a patient who survived an operation (using cardiopulmonary bypass and total circulatory arrest) to retrieve an embolized prosthetic valve.

(Ann Thorac Surg 1990;49:140–2)

In a patient with a prosthetic heart valve who experiences the sudden onset of heart failure, embolic phenomena, or other catastrophic events, the functional status of the valve should be evaluated quickly. Auscultation of the heart for prosthetic valve sounds, chest radiography, fluoroscopy, echocardiography, and cardiac catheterization have been used to diagnose prosthetic valve dysfunction [1–6]. Once the diagnosis of dysfunction is made, urgent operation is necessary. We report the successful management of dehiscence and embolization of a prosthetic aortic valve and its retrieval from the aortic arch using profound hypothermia and total circulatory arrest.

Bacterial endocarditis developed in a 25-year-old woman with a history of drug abuse in 1982, requiring emergency aortic valve replacement with a 24-mm Starr-Edwards aortic valve prosthesis. Subsequently, the patient experienced frequent recurrence of bacterial endocarditis, which was treated medically, as she repeatedly refused operation. In August 1987, she was admitted to an outside hospital for treatment of congestive heart failure. An echocardiogram showed aortic regurgitation; a paravalvular leak was not clearly demonstrated. Again she refused further evaluation and signed out against medical advice. On September 7, 1987, she was admitted to Los Angeles County/University of Southern California Medical Center complaining of pain in her right leg, and arteriogram demonstrated an embolus to that extremity. Intraarterial urokinase was started because she refused operation. Several hours later, she experienced an acute episode of chest pain and dyspnea. Within minutes her condition deteriorated, and she required resuscitation, tracheal intubation, and inotropic support.

At physical examination the prosthetic valve sounds were interpreted as normal. A chest roentgenogram showed the Starr-Edwards aortic prosthesis to be in the aortic arch (Fig 1). She was taken to the operating room and placed on cardiopulmonary bypass.

We decided to use retrograde femoral arterial cannulation for bypass because we were concerned that standard antegrade aortic perfusion might dislodge the prosthesis or provide inadequate perfusion of the craniocephalic vessels due to the location of the embolized prosthesis. We also realized that femoral cannulation might prove inadequate for a variety of reasons (ie, small femoral artery, unknown integrity of the abdominal aorta because of the embolic history, anuria for the previous few hours, and possible inability to perfuse the ascending aorta). These factors prompted us to have available the option of perfusion through either route. Therefore, we fashioned a Y arterial perfusion system to perfuse retrograde, antegrade, or both (Fig 2). Indeed, soon after bypass was started, the perfusionist reported high perfusion pressures in the femoral cannula. Consequently, we inserted the ascending aortic cannula and perfused through both routes, obtaining normal flows and pressures. This permitted us to cool the patient rapidly.

With the patient under profound hypothermia and total circulatory arrest, we opened the proximal ascending aorta obliquely as for aortic valve replacement. The embolized valve was lodged upside down in the proximal aortic arch, with the annulus of the prosthesis caught in and partially obstructing the innominate artery orifice (Fig 2). We passed a clamp through the aortotomy to the aortic arch and grasped the prosthesis. With the valve retrieved, cardiopulmonary bypass was reinstituted. Inspection of the valve showed that aortic annular tissue was still attached to the sewing ring (Fig 3). We placed pledgeted sutures circumferentially to reconstruct the annulus and inserted a 23-mm St. Jude aortic valve prosthesis.

Postoperatively, the patient did well. Gram stain and cultures of the aortic tissue attached to the Starr-Edwards prosthesis were negative. Six days later, a right below-knee amputation was required for irreversible ischemia of the right leg. She was discharged 18 days after the cardiac operation.

Approximately 6 weeks later, while at home, she experienced a cardiac arrest that prompted her admission to another hospital. She was successfully resuscitated but

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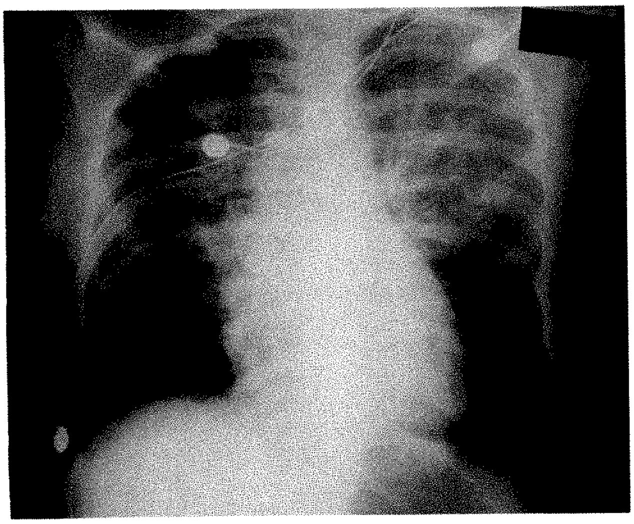

Fig 1. Chest roentgenogram shows prosthetic aortic valve inverted in ascending aorta.

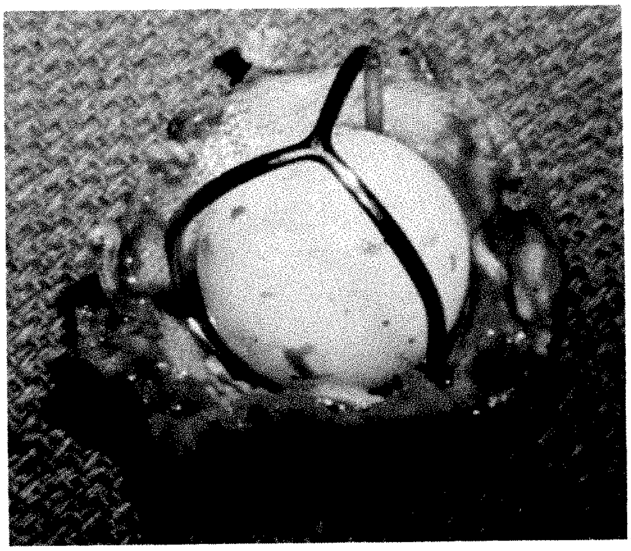

Fig 3. Aortic valve with attached annular tissue.

remained comatose for several months. A blood sample revealed both cocaine and Valium. Echocardiogram showed the prosthetic aortic valve to be functioning well. Eighteen months later, the patient remains institutionalized because of a neurological impairment secondary to the drug-induced arrhythmia and subsequent cardiac arrest. Aortic valve function remains normal.

Comment

The diagnosis of dehiscence of the aortic valve with embolization to the aortic arch was obvious on chest roentgenogram because the frame of the Starr-Edwards valve is radiopaque. In previous case reports documenting embolization of valve discs and leaflets, use of fluoroscopy, ultrasound, angiography, and computed tomographic scan often has been necessary.

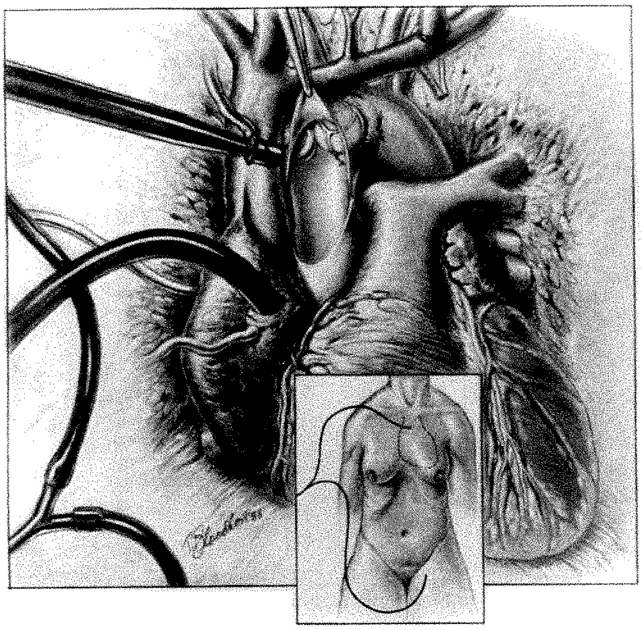

Fig 2. The embolized prosthetic aortic valve was in an inverted position in the proximal aortic arch. Arterial cannulation of both the ascending aorta and the left common femoral artery was performed (inset).

The position of the aortic valve in the proximal aortic arch posed an interesting problem. To provide adequate perfusion around the embolized valve, we had to cannulate both the femoral artery and the ascending aorta.

To retrieve the prosthetic valve from the aortic arch, we believe that the most practical method is to use profound hypothermia and total circulatory arrest. Indeed, the valve was removed rapidly and safely with this approach. Other methods that have been described for retrieving embolic discs and leaflets include removal through an aortotomy and use of a Fogarty embolectomy catheter [7].

Long-term survival is unlikely in patients who continue their drug addiction after cardiac valve replacement [8]. Our patient continued to abuse drugs even after this second valve replacement and is unlikely ever to be physically and mentally rehabilitated after the latest event.

In summary, we achieved a successful outcome after embolization of an entire prosthetic valve. Early diagnosis, proper methods for perfusion during bypass, and easy retrieval of the prosthetic valve were influential in this patient's survival. We were disturbed to learn that our patient was again abusing drugs. Cocaine had most probably caused the episode of ventricular arrhythmia and near death. The patient now is institutionalized as a result of neurological impairment incurred at the time of drug-induced arrhythmia.

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Aortic Valvoplasty for Traumatic Aortic Insufficiency: A 2-Year Follow-up

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A 23-year-old man sustained acute rupture of an aortic valve cusp in a motorcycle accident. We repaired the valve using an autologous pericardial patch. A 2-year follow-up two-dimensional echocardiogram and Doppler study show completely normal appearance and function.

(Ann Thorac Surg 1990;49:143–4)

Although rare, traumatic nonpenetrating aortic insufficiency is the most common valvular lesion in patients surviving blunt trauma to the heart. [1, 2]. Of 28 reported patients, only 4 underwent primary valve repair [3–6]. In this report, we discuss the mechanism and pathogenesis of the lesion and describe a simple method of primary repair with autologous pericardium.

A previously healthy 23-year-old man involved in a motorcycle accident was brought to the hospital unconscious. His blood pressure was 80/60 mm Hg, his pulse rate was 140 beats per minute, and his respiratory rate was 40 per minute. Neurological examination suggested intracranial injury. His heart sounds were normal and without murmurs.

After endotracheal intubation and volume expansion, he was transferred to Toronto General Hospital. His blood pressure was 130/70 mm Hg, and he was semiconscious. Chest roentgenogram revealed a widened mediastinum. A computed tomographic scan and aortogram were both normal. Laparotomy revealed lacerations of the liver and multiple serosal tears of the bowel.

A murmur suggesting aortic insufficiency was first heard six days after admission and after the patient was weaned from the ventilator. No heart failure was noted. The differential diagnoses were traumatic aortic regurgitation or valve disruption owing to subacute bacterial endocarditis.

A Doppler study revealed 3+ aortic insufficiency. The two-dimensional echocardiogram showed an echolucent space within the proximal septum, through which there appeared to be high-velocity flow. For better definition, a magnetic resonance imaging scan was performed. The images were taken in the short-axis and long-axis views of the heart, and showed a signal void area in the upper septum, continuous with the right aortic sinus of Valsalva, that demonstrated reentry of this defect back into the left ventricle. Cardiac catheterization confirmed moderately severe aortic regurgitation. Due to the patient's doubtful neurological status, cardiac operation was deferred for 3 months.

Upon examining the aortic valve, we noted that a portion of the base of the right coronary cusp (Fig 1) was separated from the aortic annulus, causing the aortic regurgitation. Inspection below the right aortic cusp revealed a tract leading from an endocardial disruption toward and into the membranous septum but not reaching the interior of the right ventricle (Fig 2). This corresponded precisely to the signal void area noted on the magnetic resonance imaging scan. The aortic valve cusps were otherwise normal. The defect at the base of the right coronary cusp was repaired using a circular patch of autologous pericardium (Fig 3); the cusp was then retracted anteriorly, exposing the endothelialized cavitation into the ventricular septum. This was closed with two pledgetted mattress sutures of 2-0 Tycron.

A two-dimensional echocardiogram performed 3 weeks later revealed normal aortic valve motion with no regurgitation or evidence of left to right shunt. Follow-up two-dimensional echocardiogram and Doppler study 2 years later showed a normal-appearing valve with no evidence of aortic insufficiency.

Comment

The mechanism of nonpenetrating rupture of the aortic valve is believed to be a sudden increase of intraaortic pressure at the time of impact, particularly during early diastole when the pressure differential across the aortic valve is maximal. The presence of partial disruption and cavitation of the interventricular septum (in our patient and in the patient reported in [3], in whom dissection continued toward the anterior leaflet of the mitral valve), explains how some cases may result in aortic regurgitation only, whereas in more severe cases complete rupture of the interventricular septum or a sinus of Valsalva may occur, leading to a communication between the aorta and one of the cardiac chambers.

Cardiac injury is often overlooked in the initial assessment of a patient after trauma. If traumatic aortic regurgitation is confirmed, surgical treatment is usually indicated. Since 1955, 28 cases of repair of traumatic aortic insufficiency have been published [7]. Of these, primary valve repair was attempted in only 4 patients, with poor results: 1 patient died during operation [6], another had severe aortic regurgitation necessitating later valve replacement, 1 survived with moderate regurgitation, and 1 had complete healing of the valve [4]. Due to these poor

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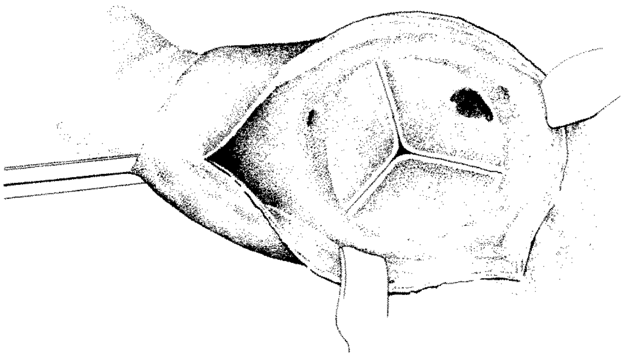

Fig 1. A portion of the base of the right coronary cusp of the aortic valve was separated from the aortic annulus.

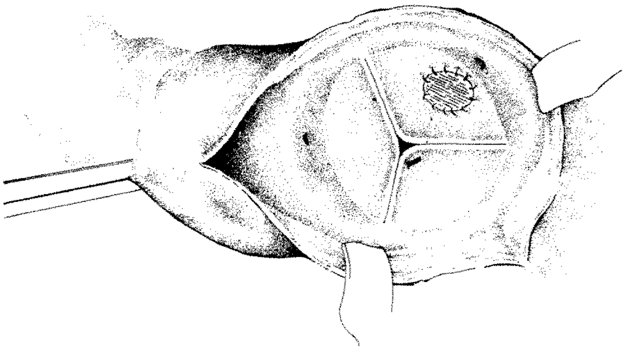

Fig 3. The defect at the base of the right coronary cusp was repaired using a circular patch of autologous pericardium.

results, valve replacement is often performed [8]. The favorable anatomical findings in our patient led us to attempt a primary repair. Furthermore, the aortic insufficiency was well tolerated and operation was delayed due to the head injury, allowing fibrous edges to facilitate repair. We are greatly encouraged by the completely normal appearance of this repaired valve by two-dimensional echocardiography 2 years later and therefore recommend attempts at direct repair whenever the pathological anatomy is favorable.

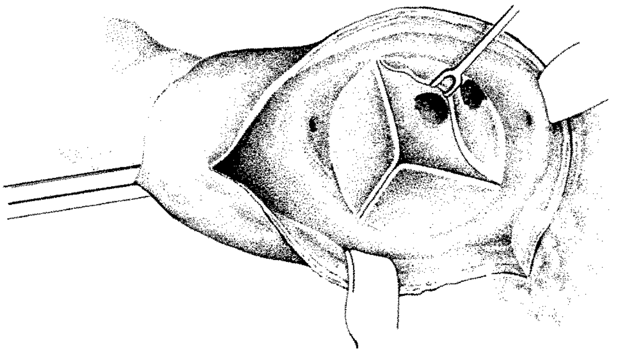

Fig 2. Inspection below the right aortic cusp revealed a tract leading from an endocardial disruption toward and into the membranous septum but not reaching the interior of the right ventricle.

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Right Atrial Thrombosis: Association With Constrictive Pericarditis

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We report a 73-year-old man with right atrial thrombosis associated with both constrictive pericarditis and persistent sinus rhythms of the heart who successfully underwent thrombectomy and pericardiectomy.

(Ann Thorac Surg 1990;49:145–6)

Right atrial mural thrombosis is quite rare and is seldom diagnosed antemortem [1]. Lethal complications of pulmonary embolism, severe right heart failure, or both, frequently develop in this lesion [2]. We report a patient with right atrial thrombosis associated with tuberculous constrictive pericarditis for whom thrombectomy together with pericardiectomy was performed.

A 73-year-old man with hypertension was admitted to our hospital on March 1, 1988, because of progressive exertional dyspnea for more than 6 months. His blood pressure was 140/100 mm Hg, and his pulse rate was 100 beats per minute. Cervical venous distention, which did not disappear in a sitting position, severe hepatomegaly, and bilateral pretibial edemas were noted. Neither cardiac murmurs nor respiratory rales were audible. Chest roentgenogram showed dullness of bilateral costophrenic angles with mild interlobal pleural effusion. Echocardiogram demonstrated a 49% left ventricular ejection fraction and dilatation of the right atrium. Contrast computed tomography confirmed a low-density area, 2 cm in diameter, in the right atrium (Fig 1) and noncalcified severely thickened pericardium. Cinemagnetic resonance imaging also showed a low-signal area as detected by computed tomography and immobile thickened pericardium. Pulmonary scintigram showed no perfusion defects. Cardiac catheterization revealed similarly elevated mean right atrial, right and left ventricular end-diastolic, and pulmonary artery wedge pressures, which were 18, 19, 20, and 17 mm Hg, respectively. A "dip and plateau" pattern was noted in both ventricles. The cardiac index was 1.7 L/min/m^2. The findings on coronary arteriogram were normal. Thus, the diagnosis of a right atrial mass associated with constrictive pericarditis was made.

On April 7, 1988, standard pericardiectomy was performed through median sternotomy and ultrasonography showed the right atrial mass. Under cardiopulmonary bypass, the mass, 2 × 1.5 × 0.8 cm in size, was visualized through a right atriotomy attaching to the atrial pectinate muscle anterolaterally (Fig 2) and was easily detached. Pathological examination proved tuberculous pericarditis, and the mass was a fibrinous thrombus. The patient was given antitubercular agents and is free of symptoms 10 months after operation.

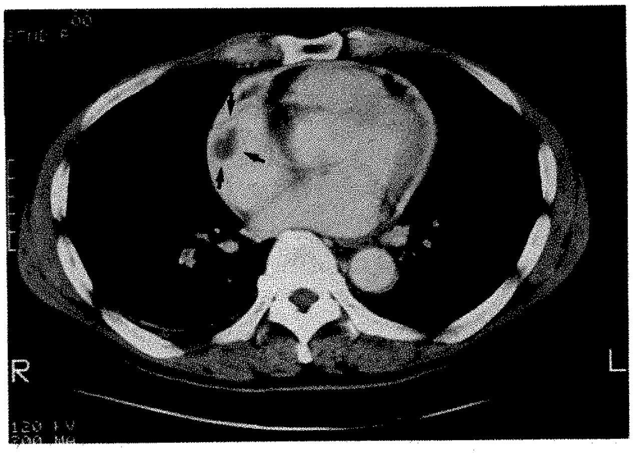

Fig 1. Contrast computed tomography shows a low-density area in the right atrium (arrows) and noncalcified severely thickened pericardium.

Comment

Right-sided cardiac thrombosis occurs very rarely except when some intracardiac foreign bodies coexist. Right atrial thrombus has been found in patients with dilated cardiomyopathy, restrictive cardiomyopathy due to amyloidosis, idiopathic enlargement of the right atrium, infective endocarditis, and endocardial fibroelastosis. Our patient is an unusual case in that right atrial thrombus was visualized in the state of sinus rhythms of the heart with constrictive pericarditis, although 1 similar previously reported case with atrial fibrillation [3] is described in the English-language literature.

Two main causes of intracardiac thrombi include hemostasis and endocardial injury of the heart. In constrictive pericarditis, impairment of filling of the ventricles during diastole causes intracardiac hemostasis, which is considerably worsened by the complication of atrial fibrillation, in turn causing thrombus formation. In addition, myocarditis in association with pericarditis leads to an endocardial inflammatory process [4], also facilitating

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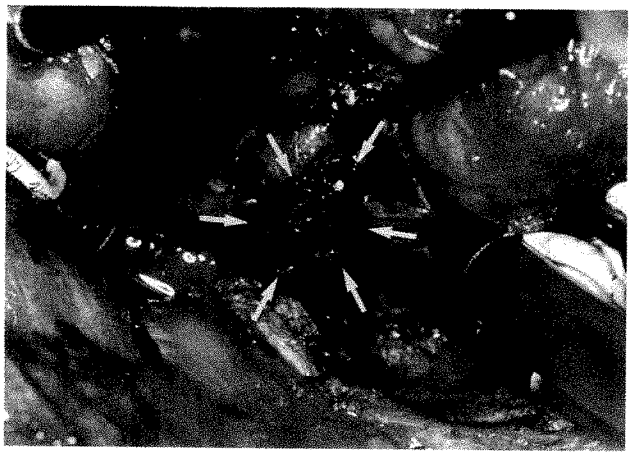

Fig 2. A thrombus (arrows) *exposed through right atriotomy attaching to the pectinate muscular endocardium of the anterolateral wall apart from the appendage of the right atrium.*

thrombosis. Our patient, despite having been in sinus rhythm, demonstrated severe hemostasis, which is considered to have contributed greatly to thrombus formation together with atrial endocardial inflammation.

Chakko and Richard [2] reported that 24 of 30 (80%) autopsied patients with right-sided cardiac thrombi had pulmonary embolism. Our study of 20 previously reported patients with primary atrial thrombosis showed that 12 (60%) had pulmonary embolism, and 6 of them died. Three others had thrombotic incarceration in the tricuspid annulus and severe cardiac failure, and all died. The total mortality rate of these 20 cases was as high as 45%. Thus, in patients with right atrial thrombi, both the incidence of pulmonary embolism and the mortality rate are considered very high. Instability of the right atrial thrombus, as confirmed in our patient, increases the risk of its spontaneous detachment from the atrial wall and makes anticoagulant therapy unsatisfactory. Early surgical thrombectomy together with standard pericardiectomy is considered the procedure of choice.

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Successful Surgical Management of Bronchial Dehiscence After Single-Lung Transplantation

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A case of bronchial dehiscence despite bronchial omentopexy is described in a patient nine days after single-lung transplantation. Rethoracotomy was undertaken as soon as the diagnosis was established before superinfection occurred. Necrotic bronchus was excised, with the anastomosis sited distally on the donor bronchus. The omentum was necrotic, and the new anastomosis was wrapped with a vascularized pedicle of pericardium. Six months after this procedure, the patient remains well.

(Ann Thorac Surg 1990;49:147–9)

Single-lung transplantation is now a realistic therapeutic option for carefully selected patients with end-stage pulmonary fibrosis [1, 2]. Early attempts at single-lung transplantation resulted in no long-term survivors; most patients who survived more than 2 weeks died of bronchial anastomotic dehiscence [3]. This occurred because isolated lung transplants (both single and double) are unique among solid organ transplants in not receiving a systemic blood supply. The recipient bronchus receives an adequate blood supply directly from bronchial arteries, and the intrapulmonary bronchus is reasonably well served by pulmonary collaterals. The intervening portion of bronchus, including the anastomosis, is rendered critically ischemic for at least 12 days until revascularization occurs from the recipient bronchial arteries [4]. Introduction of the omentum as a vascularized pedicle to wrap around the bronchial anastomosis promotes early revascularization and anastomotic healing [5] and is now a routine practice in single-lung transplantation [6]. We describe a case of bronchial dehiscence that occurred despite bronchial omentopexy and that was successfully managed by prompt surgical intervention.

A 54-year-old man with progressive cryptogenic fibrosing alveolitis, unresponsive to immunosuppressive therapy, was accepted for single-lung transplantation. Before transplantation, he was successfully weaned from steroid therapy. When a suitable donor became available, he underwent an uneventful single left lung transplantation without the need for cardiopulmonary bypass. Although he had previously undergone appendectomy for perforated appendicitis associated with generalized peritonitis, the dissected omental pedicle was believed to be satisfactory. The donor bronchus was trimmed two cartilage rings proximal to the upper lobe bronchus.

Early lung function, assessed radiologically and by alveolar-arterial oxygen gradient, was excellent. The patient was extubated 12 hours postoperatively and breathing room air by 72 hours with arterial oxygen tension of 12.4 kPa.

On day 4, he suffered an acute dyspneic episode, associated with a decrease in oxygenation and with hemodynamic instability. Immediate transbronchial lung biopsy demonstrated histological evidence of both perivascular and bronchial rejection (Fig 1). The bronchial mucosa was edematous and inflamed, with fragments of necrotic slough in the mucosal biopsy specimen. He responded rapidly and completely to a three-day course of pulsed intravenous methylprednisolone (10 mg/kg/day). Bronchoalveolar lavage excluded pulmonary infection.

However, on day 9, he again became unwell, and chest radiography revealed an obvious pneumopericardium (Fig 2). Fiberoptic bronchoscopy showed circumferential necrosis 1 cm long immediately distal to the anastomosis, although no perforation was observed. The patient underwent thoracotomy. The omental pedicle was dusky and loosely adherent. After removal of the omentum, the necrotic bronchus was excised and healthy bronchus was reanastomosed directly with interrupted polypropylene sutures. This suture line lay at the level of the bifurcation of the donor left main bronchus. Adequate oxygenation during this period of bronchial reconstruction was ensured by the use of high-frequency jet ventilation of the left lung in addition to intermittent positive-pressure ventilation of the right lung accomplished through a catheter passed down the left bronchial limb of the double-lumen endotracheal tube and across the anastomosis into the distal bronchial tree. Jet ventilation of one lung and conventional ventilation of the other has been described previously [7], and use of this technique avoided the need for cardiopulmonary bypass, which otherwise would have been essential.

A vascularized flap of pericardium was wrapped around the new anastomosis. Fluid from pleural and pericardial cavities and from the mediastinum grew scanty amounts of *Candida albicans* but was otherwise sterile.

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The patient's clinical state allowed extubation 14 hours postoperatively. After operation, the patient made a slow but steady recovery and was discharged from the hospital 22 days later. Postoperative bronchoscopy demonstrated a patent airway with healthy bronchial mucosa in the region of the anastomosis.

At follow-up 6 months later, the patient is fully rehabilitated and has excellent pulmonary function. Fiberoptic bronchoscopy was performed 5 months postoperatively after a temporary decrease in spirometry suggested lung rejection. The anastomosis was pink and well vascularized with no evidence of stenosis.

Comment

The greater omentum is probably the ideal vascularized pedicle and has a role in a number of complex problems in the chest [8]. Its use has been crucial to the success of single-lung transplantation in the modern era [1]. It is not an infallible guarantor of bronchial integrity, however, as demonstrated by this case. In particular, previous abdominal operation may make development of a suitable pedicle difficult or impossible. In addition, there is the risk of torsion and compression as the pedicle passes through the diaphragm.

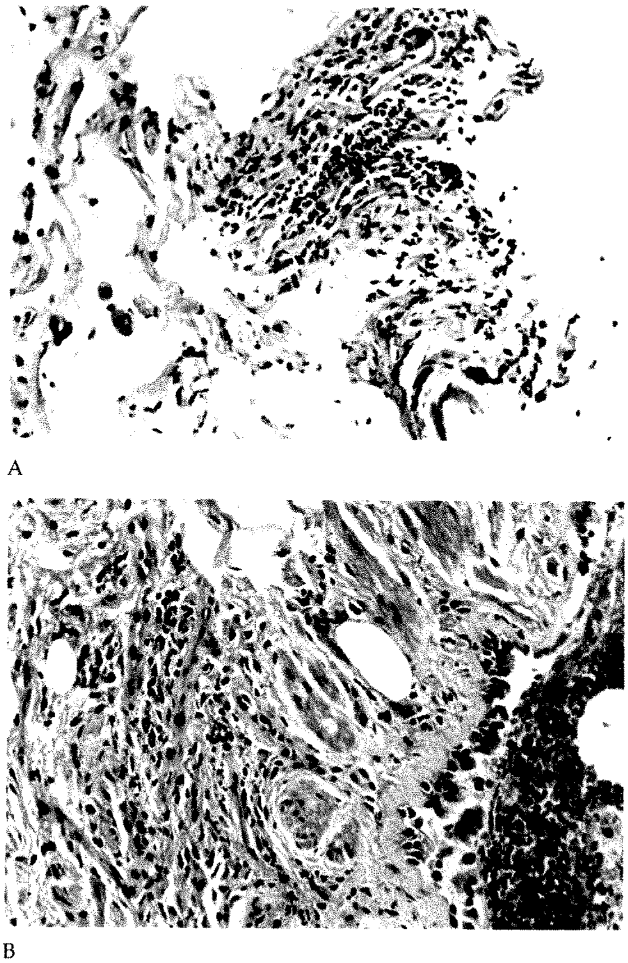

Fig 1. (A) A focus of perivascular lymphocytic infiltration in lung parenchyma. (Hematoxylin and eosin, ×400 before 41% reduction.) (B) Lymphocytic infiltration in bronchial muscle and submucosa. (Hematoxylin and eosin, ×400 before 41% reduction.)

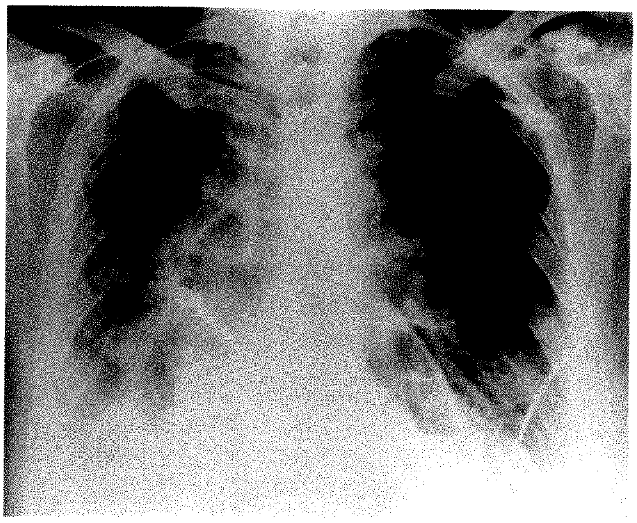

Fig 2. Chest roentgenogram shows pneumopericardium.

The already impaired bronchial healing after single-lung transplantation may be worsened by a mucosal inflammation that may accompany pulmonary rejection. Such a mechanism may have been important in our patient and has been suggested in another [2].

In the experimental situation, an intercostal muscle graft will ensure bronchial anastomotic integrity [9], and we have successfully used such a technique at retransplantation. The pericardial pedicle has also been described in this situation [10] and was chosen for our patient because of easy availability. Both of these approaches may be applicable when the omentum is not available.

We constructed the second anastomosis as close as possible to the lung parenchyma to ensure complete debridement of the necrotic segment. The donor bronchus at this site may receive perfusion from pulmonary-bronchial collaterals [11], and there is direct experimental evidence that siting the anastomosis distally results in better healing [12]. Introduction of steroids at day 4 for the treatment of pulmonary rejection may have been an additional insult in our patient. Use of steroids at an early stage has been associated with impaired bronchial healing [13].

Although bronchial omentopexy is an important adjunct to single-lung transplantation, it is not infallible. Should it fail, rapid intervention, reanastomosis distally in the donor bronchus, and use of an intercostal or pericardial pedicle may permit salvage of the situation. These alternative techniques should be considered when omentum is not available.

Addendum

The patient remains fit and well 15 months after operation.

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Repair of the Difficult Ventriculotomy

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A technique is described that allows the surgeon to repair the difficult ventriculotomy associated with early surgical treatment of myocardial infarction. Complications that occur as a result of suturing the friable myocardium can be avoided using both internal and external repair.

(Ann Thorac Surg 1990;49:150–1)

More than 30 years have elapsed since my colleagues and I first reported repair of an acutely perforated ventricular septum after myocardial infarction and excision of left ventricular aneurysms [1, 2]. With the present growing interest in early surgical treatment of myocardial infarction, most surgeons have encountered instances wherein repair of the left ventriculotomy has been difficult or even impossible. Most efforts have been directed at using external or surface repair. The friable nature of the necrotic myocardium after recent transmural infarction, however, may defy all attempts at repair, resulting in bleeding from suture sites. As the patient is weaned from cardiopulmonary bypass, and as intracavitary pressure recovers, sutures often disrupt. When this desperate situation occurs, more sutures and buttresses are placed, further distorting the ventricle and compromising the cardiac surface and the intracavitary volume. If it were available, the Hemopump (Nimbus Medical Inc, Rancho Cordova, CA), an axillary flow pump the size of a pencil eraser, could be implanted into the ventricular cavity to keep the pressure under control, which would allow the patient to be removed from cardiopulmonary bypass. The Hemopump, however, has not been tested yet in this situation.

Recently, we have used intracavitary placement of Dacron fabric to repair acute and chronic ventricular aneurysms, departing from former techniques that emphasized excision of the aneurysm [3, 4]. We have also used this technique—combining internal and external repair—to solve the technique problems associated with repair of the difficult ventriculotomy.

Technique

The standard ventriculotomy is made into the infarcted area of the ventricular free wall. The interior of the ventricle is examined to identify the transition zone between infarcted and normal myocardium. A patch is fashioned to replace or cover the diseased area. We prefer woven Dacron fabric for the patch; however, polytetrafluoroethylene (W.L. Gore and Associates, Flagstaff, AZ) or autologous pericardium could also be used (Fig 1). If the infarction has caused septal perforation, the patch should cover the septal defect and should extend over the infarcted myocardium and under the ventriculotomy. The patch is secured with a continuous, monofilament suture, which may be reinforced with pledgeted mattress sutures. The internal patch serves as a "boot," a concept similar to that used for repairing damaged automobile tires. Although the prosthesis has no contractile force, it stabilizes the still viable and functioning myocardium and thus enhances ventricular function. Moreover, use of the elliptical patch allows the surgeon to avoid making a linear repair of the ventriculotomy, which is anatomically incorrect and impairs cardiac function. In many instances, the resulting stress on the external repair is reduced sufficiently so that the customary external felt strips and pledgets are unnecessary to support the sutures.

This concept of internal and external repair of a ventriculotomy has improved our results in all types of left ventricular repairs. Application to acute septal perforations is recommended.

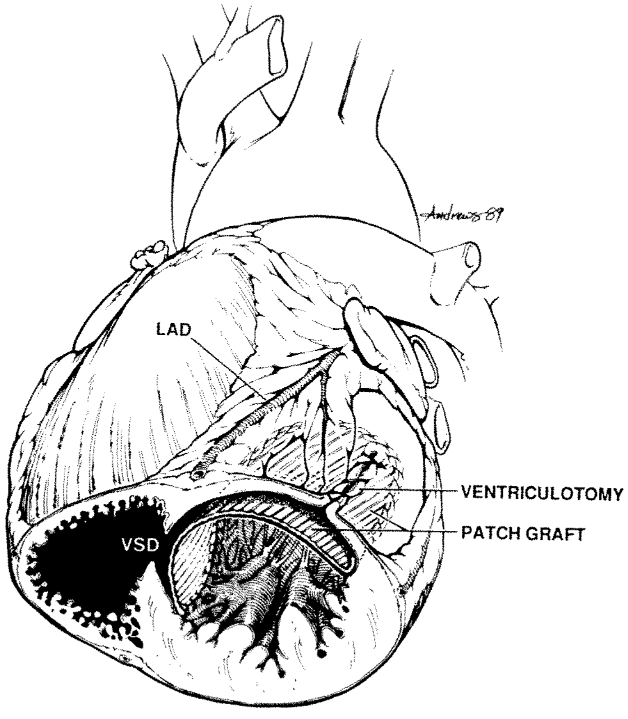

Fig 1. Internal placement of a Dacron fabric graft covering the infarcted myocardium. The patch in this instance covers a septal perforation. (LAD = *left anterior descending coronary artery;* VSD = *ventricular septal defect.)*

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REVIEW OF RECENT BOOKS

Thymic Tumors. 7th Cancer Research Workshop, Grenoble, October 1987
Edited by R. Sarrazin, C. Vrousos, and F. Vincent
Basel, Karger, 1989
172 pp, illustrated, $112.75

Reviewed by Hani Shennib, MD

Thymic tumors are always a challenging and complex subject. First, as demonstrated in this book, such tumors are uncommon. Conclusions on optimal therapy frequently depend on registries that contain only a few and far variant types of mediastinal tumors. Second, they constitute an area in which several widely ranging disciplines intersect. This book compiles current information on the epidemiology, pathology, radiology, and therapeutic strategies of thymic tumors.

Logically, the editors attempt to begin with an anatomical and histological description of the thymus. The information obtained is useful as a reference for the standard weight and cellular distribution within the normal thymus.

The chapter on presurgical evaluation of the thymus with imaging techniques is concise and clearly written. The computed tomographic figures included are very illustrative. The sections on surgical management of the thymus are quite impressive. Nowhere else can one find data collected by 14 teams from 500 patients with thymic tumors. There has been an attempt to suggest that postoperative radiotherapy, when compared with surgical resection alone, can increase the 5-year survival from 50% to 70% for invasive thymus. Based on the experience by the thymic tumor study group, the role of radiotherapy and chemotherapy for incompletely resected or advanced thymic tumors is also proposed. The outcome of treatment for stages from Ia to IV is reported.

The most intriguing parts of this book are those that relate to the pathological characterization of thymic tumors. Although definitive answers as to the exact nature and histogenesis of lymphoepithelial thymic tumors remain unclear, these chapters illustrate that differentiation and characterization of these tumors is possible. This, I believe, will have a major impact on future reporting of therapeutic outcome.

My chief criticism is in the design of the book. As most books that attempt to summarize research workshops rely on a collection of articles submitted by participants, the reader has to sometimes leap from one valley of thoughts to another. The writing style and language of writing will also vary. Nevertheless, this book constitutes an indispensable reference for those who seek in-depth knowledge of thymic tumors. I think this book is a useful addition to medical libraries.

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Method of Endoscopic Esophageal Intubation Using a Rigid Esophagoscope

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Endoscopic intubation of malignant esophageal strictures carries a substantial risk of esophageal perforation. We have developed a method of endoscopic intubation that reduces to a minimum the elements of the procedure that have to be performed "blind." The use of this method has been associated with a reduction in perforation rates when compared with other series.

(Ann Thorac Surg 1990;49:152–3)

In patients with malignant esophageal strictures who are unfit for operation, or those with anastomotic recurrence after operation, endoscopic intubation is a valuable palliative technique in the relief of dysphagia. The technique developed by Atkinson and associates [1] has become widely used, but is not without risk. Hine and Atkinson [2] reported 257 intubations with perforation occurring in 34 patients (13.2%); 26 of these perforations were esophageal and eight pharyngeal. In another series, Ogilvie and colleagues [3] reported 15 perforations in the course of 135 intubations (11.1%). Pfleiderer and associates [4] performed 31 endoscopic intubations using the Eder-Puestow technique, with esophageal perforation occurring in 3 cases (9.7%). Using the same technique, Lishman and co-workers [5] reported three esophageal perforations in 16 patients (18.8%).

Technique

The technique that we employ is similar to that described by Hegarty and associates [6]. We use a modified rigid esophagoscope that we have devised in conjunction with G.U. Manufacturing (London, UK). The endoscope differs from the traditional Negus endoscope in that it has a smoother beak while retaining its circular cross-section (Fig 1). When performing endoscopic intubation of a malignant stricture, we first carry out flexible esophagoscopy with the patient under general anesthesia to assess the caliber and length of the stricture, to measure the distance of the proximal extent of the stricture from the incisors, and to enable the appropriate length and diameter tube to be selected. The flexible instrument is then withdrawn, and the stricture is dilated with Maloney mercury-filled bougies (Pilling, Fort Washington, PA).

A 36F bougie is left in place. An Atkinson tube (Olympus Corp, Lake Success, NY) is passed over the bougie and pushed through the cricopharynx under direct vision with the aid of a laryngoscope. The rigid esophagoscope is passed over the bougie, and the beak of the instrument is engaged in the cup of the tube. The tube is pushed to the appropriate level, using the calibration on the side of the esophagoscope to measure the distance over which the tube should be advanced. The bougie and the rigid instrument are withdrawn. Flexible esophagoscopy is then performed to confirm that the tube is correctly positioned. The completed assembly of tube, bougie, and esophagoscope is illustrated in Figure 2.

Our technique differs from those previously described in several important respects. Using the method of Atkinson and associates [2] a large part of the procedure is carried out "blind," and the apparatus for introducing the tube is flexible, making it difficult to apply forward pressure accurately as it enters the stricture. The use of an Atkinson tube, however, overcomes the problems of proximal migration encountered with Procter-Livingstone tube [6], whereas the use of the flexible endoscope enables the position of the tube to be checked without having to carry out a barium swallow. In their study, Hegarty and colleagues [6] make no mention of perforation rates; however, they do report a mortality of 16.6%. We believe that our lower mortality relates to the im-

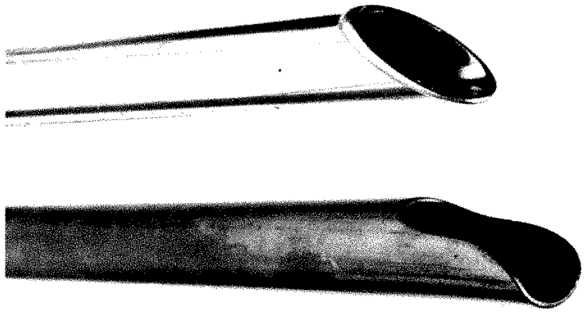

Fig 1. The modified rigid esophagoscope (top), illustrating the rounded beak that nevertheless preserves the internal diameter of the instrument.

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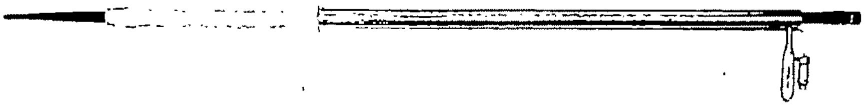

Fig 2. The completed assembly of modified esophagoscope, Maloney bougie, and Atkinson tube.

proved safety of the new esophagoscope as compared with the traditional Negus instrument.

Comment

Since taking delivery of the new esophagoscope, we have performed 37 intubations in 37 patients. Thirty-four patients were discharged from the hospital able to swallow adequately. Three patients died in the hospital, 1 as a result of mediastinitis after perforation at the gastroesophageal junction and 2 as a result of bronchopneumonia.

Having used this technique successfully in 37 patients, we report a perforation rate of 2.7%, with 91.9% of patients surviving the procedure and being discharged from the hospital. In-patient stays after the procedure ranged from one to 16 days (mean, 4.13 days). Of the 34 patients discharged from the hospital, 4 were lost to follow-up; of the remainder, none were alive 6 to 15 months later, the mean survival being 60.6 days (range, 1 to 300 days). In the course of the follow-up period, 3 patients were readmitted on a total of four occasions with tube-related problems, requiring the tubes to be unblocked or repositioned.

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The Introduction of Closed Chest Cardiac Massage

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The introduction of closed chest cardiac massage by Dr William Kouwenhoven and associates has markedly changed the outcome of patients with cardiac arrest. The fortuitous discovery of the simple yet ingenious concept of closed cardiac massage has saved countless lives. In fact the manuscript published by Kouwenhoven and colleagues has been touted "to have resulted in saving more lives than any other medical manuscript during the past century." Although newer techniques and methods of cardiac resuscitation have been developed, their successes will be measured against the technique described by Kouwenhoven and colleagues.

(Ann Thorac Surg 1990;49:154–6)

It has been approximately 30 years since Kouwenhoven and associates of Johns Hopkins University introduced the concept of closed chest cardiac massage for cardiac resuscitation after cardiac arrest or ventricular fibrillation. Before publication of this landmark article [1], cardiac resuscitation had been limited to open thoracotomy and manual cardiac massage under direct vision. This required that skilled medical personnel be in attendance in a hospital environment at the time of cardiac arrest. However, then as now, two thirds of cardiac arrests related to cardiac disease occurred outside the hospital.

Today, successful closed chest resuscitation in groups of patients with documented cardiac arrest has been accomplished in 60% to 80% of cases. Over the years, this simple yet ingenious concept of closed chest cardiac massage has saved countless lives and can be projected as saving between one hundred thousand and two hundred thousand lives per year in the United States. As noted in the article by Kouwenhoven and associates, "Anyone, anywhere can now initiate cardiac resuscitative procedures. All that is needed are two hands."

Early Work

Early efforts at cardiopulmonary resuscitation include biblical reports of a child who was revived by an adult lying on it and blowing into its mouth. Other techniques, of historical interest only, included placing the patient on a rapidly galloping horse or violently rocking the patient to supply "artificial life" [2, 3].

Before the work of Kouwenhouven and colleagues, early laboratory studies had investigated the enhancement of circulation in patients with cardiac arrest. The first laboratory investigation was reported in 1878 by Boehm [4], who was able to obtain blood pressures in cardiac-arrested cats by applying rhythmic pressure to the thorax. Tournade and co-workers [5] in 1934 also noted that abrupt and swift compressions of the canine chest resulted in blood pressures between 60 and 100 mm Hg in the cardiac arrested but ventilated dog model. The investigations of Kouwenhoven and colleagues were prompted by the early work of Gurvich and Yuniev [6], Russian physicians, and their own work [7] in Baltimore in the mid-1950s on alternating current defibrillation of hearts suffering from ventricular fibrillation. Gurvich and Yuniev [6] used a series of a capacitors to send an alternating current condenser discharge through the thorax of cardiac-arrested dogs. This charge initiated return of normal cardiac rhythm and function. These findings were published in the Russian literature but not in any English-language journals. Kouwenhoven and co-workers [7] confirmed these findings in 1957. Until Kouwenhoven's discovery, however, the preferred technique for cardiopulmonary resuscitation continued to be open thoracotomy and manual cardiac massage under direct vision.

Kouwenhoven's Work

Dr William B. Kouwenhoven (Fig 1) was, at the time his landmark article was published, a retired professor emeritus and former dean of the Engineering School at Johns Hopkins University. On retirement, he received support for his laboratory investigations into defibrillation and closed-chest cardiac massage from Dr Alfred Blalock, then chairman of the Department of Surgery at Johns Hopkins.

The concept of defibrillation of the fibrillating heart was relatively new, and many researchers reported that defibrillation was successful only if started 1 or 1½ minutes after cardiac arrest. The concept that the time frame for successful defibrillation could be extended with a period of rhythmical extrathoracic forceful compressions, and thus the entire concept of prolonged support of the cardiac arrested heart, allowing for later defibrillation, was discovered serendipitously. While testing new (and very heavy) paddles for a defibrillating machine on an unconscious animal that was hooked up to an intraarterial blood pressure monitor, Kouwenhoven and colleagues noticed that the animal's blood pressure increased merely from the weight of the paddles on its chest. Intrigued by this observation, they discovered they could keep the cardiac-arrested dog alive by rhythmically pressing on its sternum with 80 pounds of pressure once every second for 10 minutes. Assisting Kouwenhoven in the investigation on closed chest cardiac massage were Dr James Jude,

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Fig 1. Dr William Bennett Kouwenhoven's (1886–1975) original interest in cardiovascular physiology began in 1928 when, at the request of electrical power companies, he began a series of experimental studies on the effects of electrical current on the heart prompted by a critical problem in the electrical power industry: the death of linemen whose hearts were sent into irregular rhythms by electric shocks. In 1933, Kouwenhoven and colleagues discovered that the same shock could stop fibrillation and return a heart to normal rhythm. In 1947, Kouwenhoven developed an open chest defibrillating system and in 1958 the closed chest defibrillating device that is the standard of care today. Born in Brooklyn, New York, Kouwenhoven received his undergraduate and Master's degrees from the Polytechnic Institute of Brooklyn, New York, and completed his doctoral degree in electrical engineering in Germany. In 1914, he joined the staff at Johns Hopkins University in the engineering school and eventually served as dean of that school from 1938 to 1954. On his retirement, he was appointed a lecturer in surgery at the Johns Hopkins School of Medicine; he began to develop closed chest cardiac massage after he was 68 years old. In 1969, when Kouwenhoven was 83 years old, he was awarded an honorary medical degree from Johns Hopkins University, 55 years after he had joined the faculty. (Figure provided by the Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions.)

a surgical resident, and G. Guy Knickerbocker, an electrical engineer and assistant in surgery.

From this chance discovery came Kouwenhoven's original concept of closed chest cardiac massage: the heart was considered limited anteriorly by the sternum and posteriorly by the spine, with its lateral expansion constricted by the pericardium. With this "limited space" for the heart to be compressed in, it was believed that pressure on the sternum would compress the heart between it and the spine, forcing out blood. Furthermore, relaxation of this pressure allowed the heart to refill. In an elaborate series of animal experiments involving more than 100 dogs, Kouwenhoven and colleagues developed an effective method of closed chest cardiac massage that easily sustained the dogs' circulation for up to 30 minutes in ventricular fibrillation. This allowed a defibrillating shock to be delivered and immediate return of normal sinus rhythm. The clinical part of the article by Kouwenhoven and colleagues [7] contains case reports of 5 patients successfully resuscitated after cardiac arrest or ventricular fibrillation, with good return of cardiac rhythm and no neurological sequelae.

The editor's note accompanying the original article in 1960 states that use of this technique on 20 patients had achieved an overall survival rate of 70%, which can be considered identical to the survival rate today.

The original article recommended that the patient be in a supine position, preferably on a rigid board. The heel of one hand is placed on top of the sternum, the other hand is placed on top of the first hand, and firm pressure is applied downward approximately 60 times per minute. Although the rate requirement has now been changed somewhat by the American Heart Association, this description of closed chest cardiac massage has remained constant for 30 years [8].

Present and Future Cardiopulmonary Resuscitation

Although the survival rate with cardiopulmonary resuscitation has not changed significantly in the last 30 years, the physiological basis for the effective means of maintaining circulation to the heart and brain has been investigated. The term *cardiac massage* is still used in the literature today, but the concept that external chest compression results in movement of blood through direct cardiac compression has been challenged. There is now debate over whether closed chest compression results in "direct" blood flow or causes an increase in intrathoracic pressure that is transmitted to all intrathoracic vascular structures, allowing "passive" blood flow.

Although controversial issues existing today in cardiopulmonary resuscitation include the optimal rate of compressions, the duration of compression, the manipulation of airway pressures during compression, the addition of simultaneous ventilation at varying rates and durations, abdominal binders, inflatable thoracic vests, and the addition of peripheral vasoconstricting drugs among many other variables [9], these are all based on the original work. These different investigations and techniques increase our understanding of closed chest cardiac massage and perhaps increase the ability to allow survival after cardiac arrest, but they in no way decrease the importance of Kouwenhoven's original article. In fact, they only reemphasize its enormous importance. Approximately 6 to 8 million Americans have the clinical diagnosis of coronary artery disease. Cardiovascular disease accounts for nearly 1 million deaths yearly in the United States. One fifth of these deaths occur in patients younger than 65 years. Any of these patients is at risk for sudden cardiac arrest, and two thirds of such cardiac arrests occur outside the hospital. If Kouwenhoven's original survival rate of 70% can be maintained in these patients, then it can be calculated that between one hundred thousand and two hundred thousand Americans can be saved per year by his simple but ingenious innovation. Kouwenhoven's original technique of closed chest cardiac massage remains as important today as it was 30 years ago.

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Candida Mediastinitis After a Cardiac Operation

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Candida mediastinitis is a rare condition characterized by a high mortality and chronic morbidity. Including the present review, only 39 cases have been described, 67% occurring after a cardiac operation. *Candida* mediastinitis has a 55% mortality in the postoperative setting and a mortality of 92% among patients without a prior cardiac procedure. Although no patient survived *Candida* mediastinitis without surgical drainage of the mediastinum, survival was 85% among 13 patients who underwent operative mediastinal drainage. Chronic wound infection developed in 6 survivors of operative drainage without muscle flap closure, but in all patients closed with vascularized flaps, healing ultimately occurred. Aggressive surgical management with mediastinal drainage, sternal debridement, and early wound closure with vascularized flaps are essential to minimize the otherwise high morbidity and mortality of *Candida* mediastinitis.

(Ann Thorac Surg 1990;49:157–63)

Though the overall mortality from cardiac operations has greatly decreased in recent years [1], postoperative mediastinitis remains a life-threatening complication in 1% to 2% of patients [2–5]. Of all types of mediastinitis, *Candida* mediastinitis may be a phenomenon of increasing frequency [6], and it has an unusually high morbidity and mortality. Optimal management of postoperative *Candida* mediastinitis remains unclear and merits reevaluation.

Illustrative Case Reports

Patient 1

A 42-year-old man was admitted for progressive pedal edema and dyspnea after coronary artery bypass grafting. He had insulin-dependent diabetes, and 10 weeks before admission, he had undergone coronary artery bypass grafting, which was complicated by postoperative exploration for mediastinal bleeding. Three weeks postoperatively, a low-grade fever and sternal wound drainage had developed and persisted despite intravenous and oral administration of antibiotics.

Ten weeks after coronary artery bypass grafting, the patient was hospitalized with induration and tenderness over the lower sternum, an S_4 gallop, ascites, and 4+ pitting edema of both lower extremities. Cardiomegaly and bilateral large pleural effusions were present on the chest roentgenogram (Fig 1A). The leukocyte count was 11,900/mL, and the echocardiogram demonstrated a large pericardial effusion, which was confirmed on the computed tomographic scan (Fig 2). Right heart catheterization revealed equalization of right-sided pressures consistent with cardiac tamponade.

Fourteen weeks postoperatively, an anterior thoracotomy was performed through the left fifth intercostal space to treat persistent cardiac tamponade. A window of pericardium was excised, and several hundred milliliters of purulent pericardial fluid was evacuated. Histological examination showed acute and chronic pericarditis, and the pericardial fluid culture grew *Candida albicans.* After the chest tube was removed from the pericardial space on the eighth postoperative day, the patient began a 4-week course of intravenous amphotericin B with a total dose of 1 g. Five weeks after drainage, he was discharged afebrile (Fig 1B).

Three weeks after discharge, chronic drainage from the lower portion of the sternal incision developed. Wound cultures grew *C albicans*. The patient was treated with wound debridement, excision of the xiphoid process, and 1 g of intravenous amphotericin B followed by 3 weeks of intravenous cefoperazone sodium and 4 weeks of oral 5-fluorocytosine. When the sternal wound infection recurred 16 months after the coronary bypass procedure, he underwent debridement of the lower sternum and right costal cartilages with flaps of the pectoralis and rectus muscles to cover the wound. At present, 28 months after the original operation, the wound has been fully healed for more than 9 months.

Patient 2

A 62-year-old-man with insulin-dependent diabetes was evaluated for fever, leukocytosis, and cardiomegaly 25 days after coronary artery bypass grafting. In the immediate postoperative period, cardiac tamponade was suspected and was treated by opening the lower 4 cm of the sternal wound and placing a chest tube into the pericardial space for two days. *Serratia marcescens* pneumonia also developed, necessitating tracheostomy and treatment with amikacin sulfate and piperacillin sodium.

On the 25th postoperative day, he was again febrile (38.8°C orally). Physical examination was remarkable for a pulse rate of 110 beats per minute and an open, granulating wound over the lower 4 cm of the sternotomy incision. The chest roentgenogram showed cardiomegaly and a left pleural effusion (Fig 1C). The leukocyte count was 29,000/mL, and the echocardiogram showed an anteroap-

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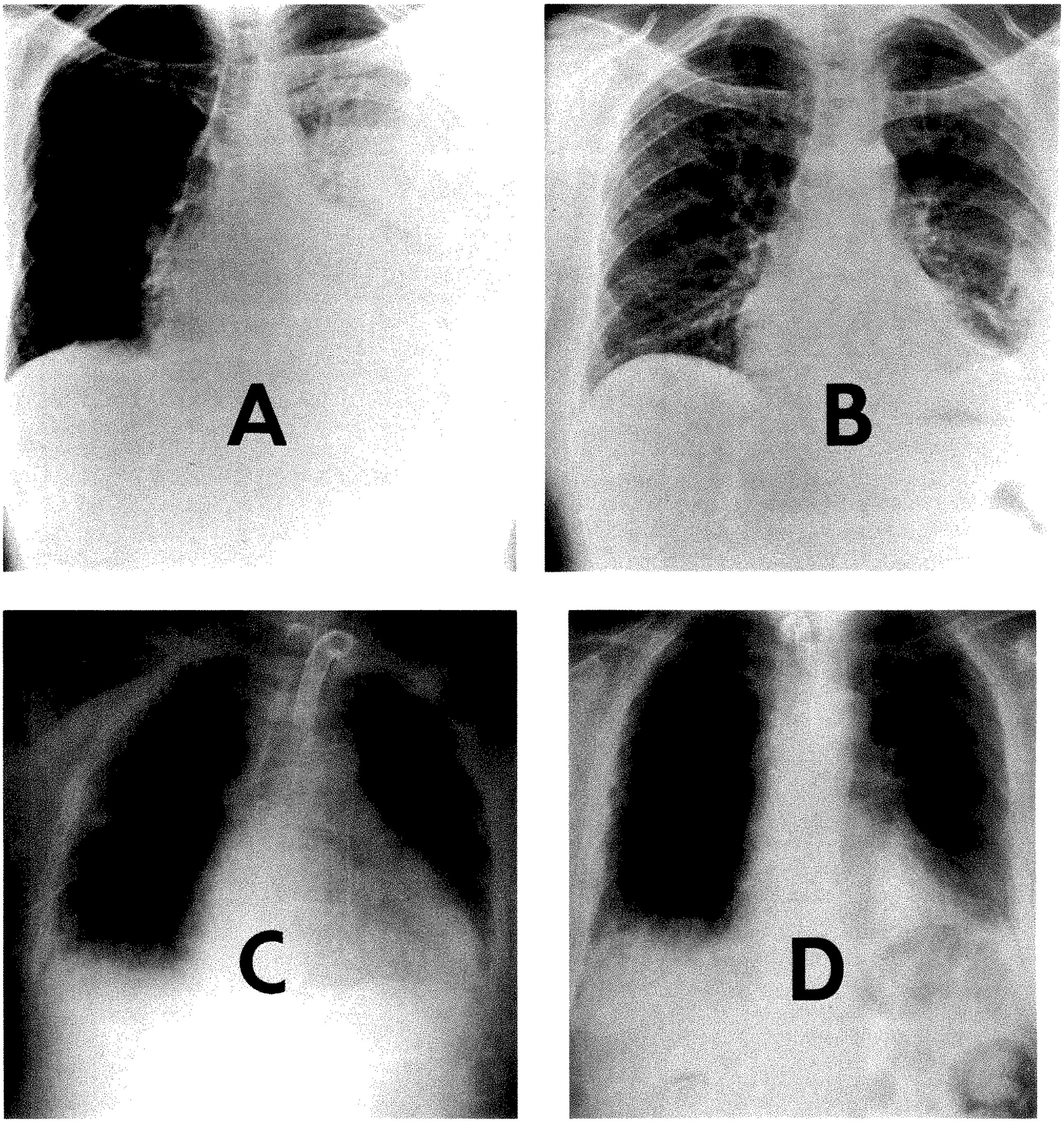

Fig 1. (Patient 1.) (A) Preoperative chest roentgenogram and (B) roentgenogram made 5 weeks postoperatively. (Patient 2.) (C) Preoperative chest roentgenogram and (D) roentgenogram made 5 weeks postoperatively.

ical pericardial effusion. Needle pericardiocentesis produced fluid, which subsequently grew *C albicans*. A regimen of intravenous amphotericin B was begun. On the 28th postoperative day, the patient underwent an anterior thoracotomy through the left fifth intercostal space, and 300 mL of free pericardial fluid was drained. A chest tube was left in the pericardial space for eight days postoperatively. The patient completed a 5-week course of intravenous amphotericin B with a total dose of 1 g (Fig 1D).

After discharge, the patient continued to drain from the thoracotomy and sternal incisions necessitating debridement of the xiphoid process, several suture abscesses, and infected sternal wires at 7, 12, and 15 months postoperatively. He underwent further sternal debridement and wound closure with a pectoralis muscle flap 19 months postoperatively. At last follow-up 37 months after the initial coronary bypass procedure, the wound had been fully healed for longer than 12 months.

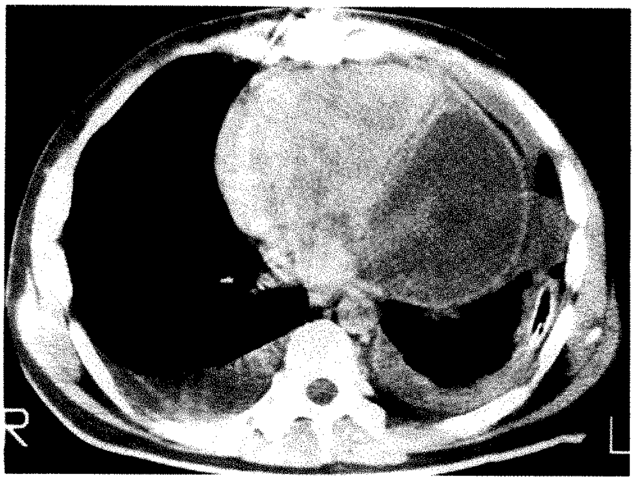

Fig 2. (Patient 1.) Preoperative computed tomographic scan of the chest demonstrating a large posterolateral pericardial effusion.

Comment

A review of the English-language literature revealed 37 patients with culture-proven *Candida* mediastinitis (Tables 1, 2). The earliest case of *Candida* mediastinitis was reported in 1967 [7], most having been reported in the last 15 years. The increased occurrence of *Candida* mediastinitis coincided with the growing volume of cardiac operations, and all but 13 cases followed a cardiac surgical procedure. Although mediastinitis has been clinically recognized since the 1920s, most cases of mediastinitis before the era of cardiac surgery involved mixed flora and gastrointestinal perforation [25]. The absence of *Candida* mediastinitis in earlier reports may also have followed inadequate fungus culture techniques, reduced awareness of *Candida* as a mediastinal pathogen, and less use of broad-spectrum antibiotics [6].

In the postoperative period, *Candida* caused 5% of all mediastinitis reported in the larger series (Table 3). The case of patient 2 presented here is the only known case of *Candida* mediastinitis occurring at Duke University Medical Center in the past 8 years. A recent 2-year review of mediastinal infection after cardiac operations here yielded 26 cases (1.18%) of mediastinitis in 2,195 patients. *Candida* was the primary pathogen in none, although later fungous superinfection did occasionally occur after antibiotic therapy. Series reporting *Candida* in as many as 12% of patients with mediastinitis usually involved patients with closed-wound irrigation, which had a higher incidence of *Candida* mediastinitis [3, 6].

Table 1. Summary of Data on 26 Patients With Candida *Mediastinitis After a Cardiac Operation*

Reference	Publication Year	Age (yr)	Sex	Procedure	Treatment	Outcome	Chronic Wound Infection
McConnell and Roberts [7]	1967	26	M	AVR	None	Died	. . .
Bryant et al [8]	1969	47	M	AVR	Closed irrigation	Lived	No
Gaines and Remington [9]	1972	. . .	. . .	. . .	. . .	Died	. . .
		. . .	. . .	. . .	. . .	Died	. . .
Sanfelippo and Danielson [10]	1972	. . .	. . .	Median sternotomy	Closed irrigation	. . .	. . .
		. . .	. . .	Median sternotomy	Closed irrigation	. . .	. . .
Engelman et al [6]	1973	53	M	AVR	Closed irrigation	Lived	Yes
		67	F	MVR, AVR, CABG	None	Died	. . .
		55	F	MVR	Closed irrigation	Died	. . .
		55	M	CABG	Closed irrigation, open debridement	Lived	Yes
Rubin and Moellering [11]	1975	. . .	. . .	. . .	None	Died	. . .
		. . .	. . .	. . .	None	Died	. . .
Thomas et al [12]	1977	52	M	CABG	Open debridement, flap	Lived	Yes
Walsh and Hutchins [13]	1980	6 wk	F	PA banding	None	Died	. . .
Kinnard et al [14]	1984	. . .	. . .	Median sternotomy	Open debridement	Lived	Yes
Pairolero and Arnold [15]	1984	. . .	. . .	Median sternotomy	Flap	Lived	. . .
		. . .	. . .	Median sternotomy	Flap	Lived	. . .
		. . .	. . .	Median sternotomy	Flap	Lived	. . .
Cheung et al [2]	1985	. . .	F	MVR	. . .	Died	. . .
Rutledge et al [4]	1985	. . .	. . .	Valve replacement	. . .	Died	. . .
		. . .	. . .	Valve replacement	. . .	Died	. . .
		. . .	. . .	Valve replacement	. . .	Died	. . .
Majure et al [16]	1986	. . .	. . .	Median sternotomy	Flap	. . .	. . .
		. . .	. . .	Median sternotomy	Flap	. . .	. . .
Glower et al [present report]	1990	42	M	CABG	Flap	Lived	Yes
		62	M	CABG	Flap	Lived	Yes

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; PA = pulmonary artery.

Table 2. Summary of Data on 13 Patients With Candida *Mediastinitis Not After a Cardiac Operation*

Reference	Publication Year	Age (yr)	Sex	Surgical Setting	Drainage	Outcome
Bernhardt et al [17]	1972	46	F	Biliary operation	No	Died
Law et al [18]	1972	8	F	Burn	No	Died
		7		Burn	No	Died
Rubin and Moellering [11]	1975	. . .	. . .	Leukemia	No	Died
		. . .	. . .	Gastric operation	No	Died
Ihde et al [19]	1978	. . .	. . .	Cancer	. . .	Died
		. . .	. . .	Cancer	. . .	Died
Scully et al [20]	1979	66	M	Cancer	No	Died
Eng et al [21]	1981	39	M	Alcoholism	Yes	Died
Geisler et al [22]	1981	30	M	Leukemia	Yes	Lived
Gronemeyer et al [23]	1982	77	F	Hodgkin's disease	No	Died
Kraus et al [24]	1988	61	M	Steroids	No	Died
		74	F	Erythroleukemia	No	Died

The age of patients who had *Candida* mediastinitis after a cardiac operation ranged from 6 weeks to 67 years (median age, 55 years), and 64% of patients were male (see Table 1). Cardiac surgical procedures involved pulmonary artery banding (1 patient), valve replacement (9 patients), and coronary artery bypass grafting (4 patients). These patients became symptomatic from six days to 3 weeks postoperatively (median time, 12 days). In at least 4 patients, cultures from the mediastinum grew organisms in addition to *Candida*, with fungus often being identified later in the clinical course [2, 6, 8].

Patients in whom *Candida* mediastinitis developed for other reasons tended to be younger; age ranged from 7 to 77 years (median age, 46 years) (see Table 2). Included in Table 2 are all patients with *Candida* demonstrated in the extracardiac mediastinum, excluding isolated endocarditis or myocarditis. In all patients, mediastinal involvement was demonstrated in the pericardium only. Eleven patients were immunocompromised either by cancer (7 patients), burn (2 patients), steroids (1 patient), or alcoholism (1 patient). Two patients had undergone recent abdominal surgical procedures. In 3 patients, cultures grew *Candida tropicalis* [20, 23, 24]; in all the others either with or without a prior cardiac operation, the organism was either *C albicans* (13 patients) or an unspecified *Candida* species. Although at least 9 of the 13 patients who had *Candida* mediastinitis and had not undergone operation had systemic candidiasis [17–20, 23], mediastinal or pericardial involvement in systemic candidiasis was relatively uncommon. Ihde and colleagues [19] found pericardial infection in only 2 of 168 patients with candidiasis and cancer on whom a postmortem examination was done. Mediastinal involvement with candidiasis was noted after death in only 2 of 15 patients with burns [18] and in 3 of 37 patients with postoperative systemic candidiasis whose histories were summarized by Bernhardt and associates [17] and Gaines and Remington [9].

Table 3. Incidence of Candida *Mediastinitis in Large Series of Patients With Postoperative Mediastinitis*

Reference	Publication Year	Patients With *Candida*	% With *Candida*
Thurer et al [26]	1974	0/14	0
Grmoljez et al [27]	1975	0/10	0
Sutherland et al [28]	1977	0/13	0
Stoney et al [29]	1978	0/20	0
Herrera and Ginsburg [30]	1982	0/10	0
Kinnard et al [14]	1984	1/10	10
Pairolero and Arnold [15]	1984	3/38	8
Cheung et al [2]	1985	1/36	3
Grossi et al [3]	1985	9/77	12
Rutledge et al [4]	1985	3/29	10
Ottino et al [5]	1987	0/48	0
Verkkala [31]	1987	0/12	0
Durandy et al [32]	1989	0/11	0
Total		17/328	5.2

In this collection of all reported cases of *Candida* mediastinitis in either the postoperative or nonsurgical setting, factors associated with *Candida* mediastinitis included endocarditis and myocarditis in at least 6 patients [7, 18–20, 23, 24]. Nonetheless, pericarditis was found in only 1 of 91 patients with *Candida* endocarditis reviewed by Seelig and associates [33]. At least 2 patients with *Candida* mediastinitis had central venous catheterization for hyperalimentation [18, 20]. Broad-spectrum antibiotic exposure preceded *Candida* mediastinitis in 14 of 15 patients and may have contributed to wound colonization by *Candida* [6].

In patients with *Candida* mediastinitis, findings at presentation paralleled those cited by Grossi and coauthors [3] for mediastinitis and by Rubin and Moellering [11] for infectious pericarditis. Reported findings were fever in 8 of 12 patients, leukocytosis in 7 of 12, tachycardia in 6 of 6, cardiomegaly in 3 of 5, and pericardial rub in 1 of 6. The 2 patients described in the present review had symptoms similar to those reported in the literature. Each of the 2 patients was seen relatively later after a cardiac operation (25 days and 10 weeks), but in prior reports of either

Candida mediastinitis (see Table 1) or mediastinitis in general [6, 34], all patients had a mean presentation time of 12 days postoperatively. Both patients reported here were relatively immunocompromised as a result of diabetes, and each patient underwent early postoperative mediastinal reexploration, which is known to increase the risk of mediastinitis [8, 27].

Among the 37 reported patients with *Candida* mediastinitis, the mortality was 24 (73%) of 33; the outcome for 4 was not cited. Fifty-five percent of patients with *Candida* mediastinitis after a cardiac operation died versus 92% of patients with *Candida* mediastinitis without a prior cardiac procedure. Thus, *Candida* mediastinitis had nearly twice the 30% mortality reported for 336 patients with postoperative mediastinitis ($p < 0.05$) [2–5, 26–28, 34–37]. All survivors of *Candida* mediastinitis were treated with drainage of the mediastinum. The only survivor who had not undergone a prior cardiac surgical procedure had leukemia, and he was treated with surgical drainage of the pericardium and 3 weeks of intravenous amphotericin B [22]. The mortality among patients treated with surgical drainage was 18% (2 of 11). Two patients received amphotericin B alone and did not survive [7, 18]. The reported causes of death included sepsis in 8 patients [2, 7, 18, 21, 23, 24] and pulmonary edema [20] and bronchopneumonia [13] in 1 patient each. In patients who had not had operation, survival from the onset of symptoms ranged from 8 to 65 days with a median of 14 days.

The treatment of mediastinitis has been controversial whether the condition was primary pericarditis or postoperative mediastinitis. Primary bacterial pericarditis has been successfully treated with antibiotics combined with repeated pericardiocenteses [38] and with antibiotics combined with surgical drainage of the pericardium [39, 40]. Good results have been reported from surgical drainage of purulent pericarditis using median sternotomy [39], subxiphoid incision [40], or anterior thoracotomy [41].

Postoperative mediastinitis has been treated by open drainage [3, 27], wound debridement and reclosure with [8] or without [3, 32] closed-wound irrigation, and wound debridement followed by omental [42] or muscle flap closure [36]. Regardless of technique, all authors have stressed the need for adequate surgical debridement of infected bone and cartilage. Only debridement followed by omental or muscle flap closure substantially reduced the incidence of recurrent wound infection after treatment of mediastinitis (Table 4).

In contrast to the 22% incidence of chronic wound infection for mediastinitis in general, the risk of chronic wound infection for *Candida* mediastinitis after a cardiac operation was significantly increased to 86% or 6 of 7 survivors ($p < 0.01$) (see Table 1). Difficulty in eradicating wound infection after *Candida* mediastinitis can be attributed to several factors. Although antibiotics alone can cure hematogenous *Candida* osteomyelitis in 87% of patients [43], the rate of cure without surgical debridement was much lower when osteomyelitis originated from contiguous sites in the postoperative period [44]. Because of the relative avascularity of cartilage, surgical debridement might be especially important in treating chondritis [45]. Williams and colleagues [46] reported that postoperative chondritis was refractory to medical management but cleared with surgical debridement in 6 of 7 patients. Of interest, *C albicans* was the responsible organism in 4 patients, and 3 required several months and an average of four additional debridements for complete healing. Implanted foreign material and impairment of sternal vascular supply [47] associated with median sternotomy can also contribute to chronic infection in patients with postoperative mediastinitis.

Table 4. Incidence of Recurrent Wound Infection After Treatment of Postoperative Mediastinitis[a]

Reference	Publication Year	Open Drainage	Closed Drainage	Flap Closure
Thurer et al [26]	1974	. . .	2/14	. . .
Grmoljez et al [27]	1975	8/11	. . .	. . .
Barois et al [34]	1978	. . .	10/15	. . .
Stoney et al [29]	1978	. . .	3/20	. . .
Herrera and Ginsburg [30]	1982	. . .	. . .	0/10
Pairolero and Arnold [15]	1984	. . .	. . .	5/38
Cheung et al [2]	1985	. . .	4/8	2/11
Grossi et al [3]	1985	8/31	15/46	. . .
Scully et al [37]	1985	. . .	1/19	1/22
Majure et al [16]	1986	. . .	. . .	0/18
Durandy et al [32]	1989	. . .	0/11	. . .
Total[b,c]		16/42 (38)	35/133 (26)	8/99 (8)

[a] Treatment was open-wound drainage, simple debridement and closed-wound drainage, or wound closure with omental or muscle flaps. [b] Numbers in parentheses are percentages. [c] The total incidence of recurrent wound infection was 59 of 274 or 22%.

Early closure of the mediastinum with vascularized tissue flaps might be especially crucial to improving survival of and decreasing chronic wound infection in patients with *Candida* mediastinitis. Just as the increasing use of muscle and omental flaps for mediastinitis has decreased the incidence of chronic wound infection (see Table 4) and has been associated with increased survival [16, 26], so all 6 patients with *Candida* mediastinitis treated with vascularized flaps survived and were free from subsequent infection. In fact, each of the 6 cases of chronic wound infection after *Candida* mediastinitis can be attributed either to no flap closure [6, 14] or to delay of flap closure for more than 1 year [12].

The role of antifungus agents as an adjuvant to operation for *Candida* mediastinitis has not been clearly demonstrated. At least 5 of 11 reported survivors received amphotericin B or 5-fluorocytosine [6, 8, 12]. One patient survived with surgical treatment alone and no antifungus therapy [6]. Although antifungus therapy is clearly indicated for candidiasis or candidemia, chemotherapy alone has been unsuccessful in fungous chondritis [46]. Until better data become available, addition of antifungus agents to surgical treatment of *Candida* mediastinitis remains an empirical adjunct in treating an otherwise difficult problem.

In summary, *Candida* mediastinitis is a rare condition with a fourfold increase in chronic wound infection and nearly twice the mortality of mediastinitis in general. However, both mortality and chronic wound infection in *Candida* mediastinitis have been substantially reduced by wound coverage with omental or muscle flaps. A combination of surgical drainage of the mediastinum, wound debridement, early wound coverage with vascularized flaps, and possibly intravenously administered antifungus therapy should be aggressively pursued to minimize morbidity and mortality in *Candida* mediastinitis.

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Surgical Techniques for Chest Wall Reconstruction

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CORRESPONDENCE

Björk-Shiley Strut Fracture and Disc Escape

To the Editor:

I found the article by Hendel [1] concerning the method of disc retrieval of an escaped Björk-Shiley disc secondary to strut fracture interesting. Another method that we describe for retrieval of a fractured Björk-Shiley disc is to extend the sternotomy incision down to the umbilicus. Usually the disc will lodge either at the aortic bifurcation or at the takeoff of the inferior mesenteric artery. At this point the disc can be palpated, then a small aortotomy made with removal of the disc [2]. This event certainly carries a high mortality rate, and as of yet very few people survive the event. I think that the key to survival is prompt diagnosis and treatment.

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Internal Mammary Artery Grafts

To the Editor:

Vander Salm and associates [1] have drawn attention to the optimal route for the internal mammary artery as a conduit for coronary artery bypass grafting. We too have mostly used the shortest routings as described.

We disagree, however, with the last of their three conclusions, stating that no routing can be conceived to revascularize more than two coronary beds with two internal mammary arteries. In our institution we have experience in several patients with the following construction:

1. Right internal mammary artery taken down as a skeletonized vessel (to increase length) through a pericardial incision immediately anterior to the right phrenic nerve and through the transverse sinus to the diagonal and left anterior descending coronary arteries.
2. Left internal mammary artery through a pericardial incision to anterolateral, obtuse, and marginal branches ending on the posterior descending coronary artery.

Using this particular method we have been able to perform complete arterial revascularization with up to six distal anastomoses (right internal mammary artery, 2; left, 4).

Therefore, we cannot agree with the conclusions reached by Vander Salm and associates; moreover, we think that complete arterial revascularization is frequently possible using both internal mammary arteries, even in extensive coronary artery disease.

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Reply

To the Editor:

Doctor de la Rivière and colleagues have clearly redemonstrated the inadvisability of authors using absolute negatives such as "never" or "no." Not only have they proved our statement "no conceivable frugality of IMA routing can allow the revascularization of more than two coronary beds" incorrect; they have also demonstrated greater imagination and surgical fortitude than we in their remarkable achievement of revascularizing all three coronary beds with in situ internal mammary artery grafts using as many as six distal anastomoses.

Although one could theoretically question the ability of two internal mammary artery grafts to supply the flow needs of the entire myocardium, if the results in the patients whom they describe are good, those results should speak for themselves.

I congratulate them on their impressive operative achievements.

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Tetracycline Pleurodesis for Persistent Air Leak

To the Editor:

I read the article by Almassi and Haasler [1] on chemical pleurodesis in the presence of persistent air leak with interest, and would like to share my experience with this procedure.

Over the last 2 years, I have performed tetracycline pleurodesis (TP) for persistent air leak on 4 patients. Tetracycline pleurodesis was done because these 4 patients were considered poor candidates for operation. The severity of air leak was graded by its occurrence: present infrequently with cough (grade 1), present every time with cough (grade 2), present with few spontaneous breaths (grade 3), present with every spontaneous breath (grade 4). The method in brief was as follows. The chest tube was taken off suction, and the tube was clamped distally. Under sterile precautions, lidocaine (250 mg, 1% solution), saline solution (20 mL), and tetracycline hydrochloride (2,000 mg, 50 mg/mL) were then injected separately at five-minute intervals. The chest tube was held up for five minutes, the distal clamp was removed, and the tube was left off suction for four hours. Severity of pain was assessed after the procedure. A check was made four hours later for the presence of air leak, and the chest tube was reattached to suction. If, 24 hours later, the air leak was not observed, the chest tube was clamped and a chest roentgenogram was obtained. The chest tube was removed if full expansion of lung was confirmed by the radiograph.

The description and results of TP in these 4 patients are summarized in Table 1. Tetracycline pleurodesis was successful in closing persistent air leak in 2 patients. In the first patient, decrease in air leak was noted within four hours, and air leak was absent after 24 hours. In the second patient, even though the air leak was infrequent, clamping of the chest tube resulted in reaccumulation of pneumothorax and lung collapse. Persistent right upper lobe pneumothorax in this patient resolved within 24 hours of TP. In the 2 patients with acquired immunodeficiency

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Table 1. Tetracycline Pleurodesis in 4 Patients

Variable	Patient No. 1	2	3	4
Age (yr)	35	71	26	45
Sex	M	F	F	M
Predisposing disease	Asthma	Old TB	AIDS, PCP, TB	AIDS, PCP, TB
Roentgenogram	Normal	RUL fibrosis	Bilateral interstitial infiltrates	Bilateral interstitial infiltrates + cysts
Severity of air leak	4	1	4	4
Duration of air leak (days)	5	17	15	13
Pain	Severe	Moderate	None	None
Result of pleurodesis	Decrease in air leak to grade 3 in four hours, no leak at 24 hours	Resolution of residual pneumothorax in 24 hours	Unsuccessful; death in 24 hours	Unsuccessful; death in 48 hours

AIDS = acquired immunodeficiency syndrome; PCP = *Pneumocystis carinii* pneumonia; RUL = right upper lobe; TB = pulmonary tuberculosis.

syndrome (AIDS), TP was not associated with pain, and it was unsuccessful in closing the air leak and associated with early mortality.

We are aware of only three other reports dealing with TP for active air leak [2–4]. Patients with *Pneumocystis carinii* pneumonia complicating AIDS frequently sustain spontaneous pneumothorax with persistent air leak [5]. Tetracycline pleurodesis has not previously been described for persistent air leaks in patients with AIDS, but our lack of success in these 2 patients may contraindicate its use in such patients. I feel that TP was unsuccessful in these 2 patients with AIDS because of lack of pleural inflammation, as both of these patients experienced no pain with TP.

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Reply

To the Editor:

We disagree with Dr Chechani that AIDS is a contraindication to chemical pleurodesis. His failure in 2 patients with AIDS and *Pneumocystis carinii* pneumonia is probably due to inadequate time allowed for the tetracycline to remain in the pleural space (five minutes) and the fact that both patients were probably preterminal, as evidenced by their demise within 48 hours after pleurodesis. In addition, there appear to have been no maneuvers carried out to distribute the tetracycline uniformly throughout the pleural space by altering the patient's position.

Our experience with 2 AIDS patients subsequent to our published report indicates that effective pleurodesis can be accomplished, although one may have to instill tetracycline in the pleural space on multiple occasions. In fact, in 1 of our patients with bilateral spontaneous pneumothorax and *P carinii* infection, the right pneumothorax required three trials of tetracycline pleurodesis before final resolution of pneumothorax and cessation of air leak was achieved. Furthermore, there is no evidence in our patients that instillation of sclerosants into the pleural space caused any kind of rapid demise, despite their altered immunological defense mechanisms.

Our only real failure with the technique described [1] has been in a patient receiving steroids. Whether a trial of vitamin A before sclerotherapy in these patients will help bring about effective chemical pleurodesis is speculative.

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Reference

1. Almassi GH, Haasler GB. Chemical pleurodesis in the presence of persistent air leak. Ann Thorac Surg 1989;47:786–7.

Must the Mitral Valve Always Be Removed During Prosthetic Replacement?

To the Editor:

Mitral prosthetic replacement may be a hazardous procedure, particularly if the patient is seen as an emergency with poorly controlled cardiac failure. At operation the stent of the prosthesis is frequently found to be incorporated within the left ventricular wall, and its removal may cause irreparable damage to the heart.

We describe such a patient whom we treated by a new technique, leaving the stent of the failing mitral prosthesis in situ and inserting within it a Starr-Edwards valve.

A 58-year-old woman had undergone mitral valve replacement with a 35-mm Carpentier-Edwards bioprosthesis for severe rheumatic valve disease in July 1979. She made an uneventful recovery and remained well until 1988, when worsening exertional dyspnea developed. Over the following 9 months, her condition deteriorated. She appeared cachectic and breathless at rest. She was in atrial fibrillation, and there was a loud pansystolic and mid-diastolic murmur at the apex and signs of biventricular failure. The chest radiograph showed cardiomegaly, pulmonary congestion, and a right pleural effusion. Cardiac catheterization showed moderate left ventricular function and only moderate mitral regurgitation. Cardiac chamber pressures (in mm Hg) were as follows: right atrium V wave, 20 (mean, 10); right ventricle, 70/15; pulmonary artery, 70/37; pulmonary capillary wedge, 35; left ventricle, 100/10; and aorta, 105/60. The mean mitral diastolic gradient was 21 with a cardiac output of 3 L and a valve area of 0.56 cm^2. These findings were consistent with severe mitral prosthetic stenosis, pulmonary hypertension, and tricuspid regurgitation. Mitral prosthetic replacement was recommended.

At operation, the prosthetic leaflets were rigid and partially calcified. The heart tissues in general were extremely friable, and the valve struts were buried within the left ventricular wall. The valve leaflets were removed with knife and rongeur until the inner aspect of the stent was free from debris. We judged that removal of the stent carried an exceptional risk of severe damage. A 6M Starr-Edwards sizer fit perfectly inside the Carpentier-Edwards stent. This valve was chosen and anchored with 12 pledgetted sutures attached to the inner aspect of the Carpentier-Edwards sewing ring. The Starr-Edwards valve was then seated and tied into place within the existing Carpentier-Edwards stent (Figs 1, 2). The heart was rewarmed and vented, and resumed beating after cardioversion from ventricular to atrial fibrillation. Good ejection was shortly evident and the patient came off bypass easily on a small dose of adrenaline and dopamine. The left atrial pressure was measured by direct puncture at 15 mm Hg and there was no evidence of mitral regurgitation.

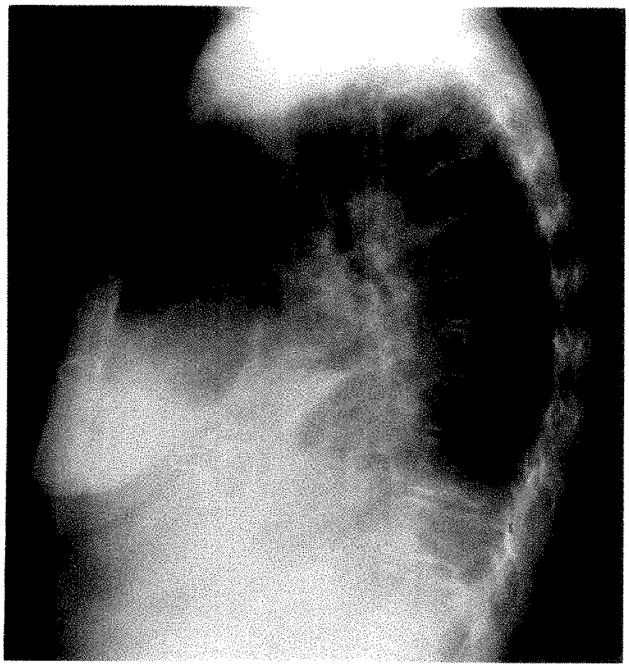

Fig 1. Preoperative lateral chest radiograph showing Carpentier-Edwards bioprosthesis in mitral position.

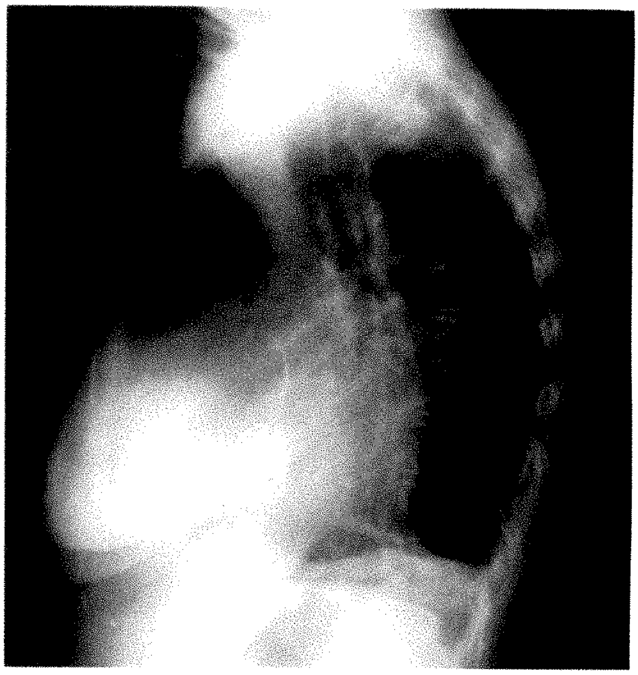

Fig 2. Postoperative lateral chest radiograph showing Starr-Edwards valve within the Carpentier-Edwards stent.

The patient made an uneventful recovery; she was ventilated for 12 hours and spent three days in the intensive care unit, during which time her small dose of inotropic agents was weaned. The patient was discharged to convalescence as routine on the tenth postoperative day without evidence of cardiac failure and with a satisfactorily functioning Starr-Edwards prosthesis. Echocardiography carried out 4 weeks postoperatively showed normal motion of the Starr-Edwards prosthesis and normal left ventricular function. Doppler studies showed a mean gradient of 5 mm Hg across the mitral prosthesis, a value similar to that obtained across a normally functioning prosthesis [1].

This technique, successful in this case, may be advantageous in those rare cases in which removal of a large prosthesis would risk serious ventricular damage.

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Reference

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Spasm of the Gastroepiploic Artery Graft

To the Editor:

I enjoyed the recent article by Mills and Everson [1]. In this article, they documented the spasm of the gastroepiploic artery (GEA) graft by postoperative angiogram. Although they reported

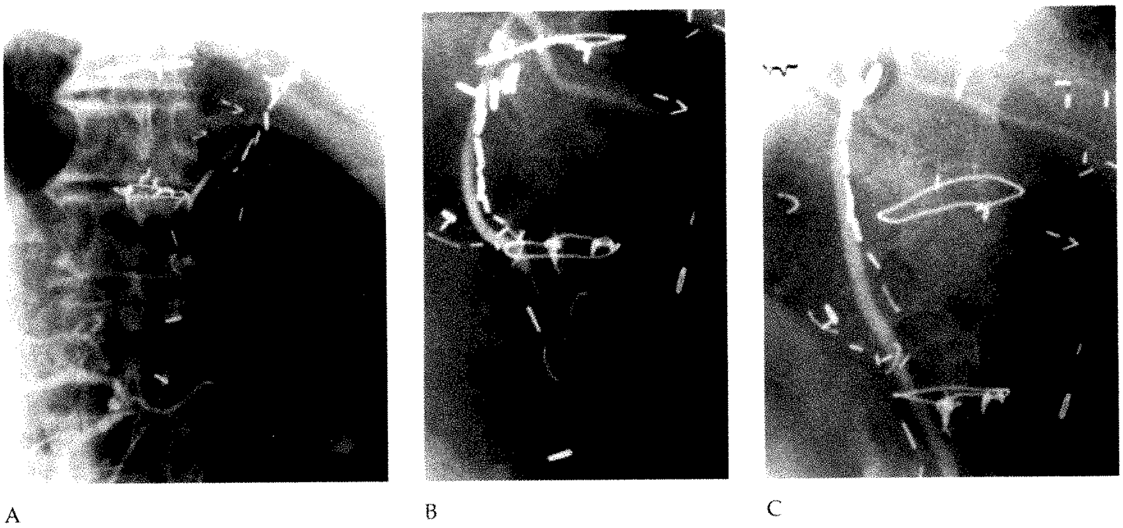

Fig 1. (A) The gastroepiploic artery (arrows) *anastomosed to the circumflex artery appears stringlike. (B) A closer view. (C) The gastroepiploic artery enlarged after nitroglycerin injection.*

the spasm only in the free GEA graft, I would like to show that it can occur in the in situ graft.

The patient was a 56-year-old man in whom the right GEA was anastomosed to the circumflex artery. The diagonal and the anterior descending coronary arteries were bypassed with the sequential left internal mammary artery graft, and the right ventricular branch and the posterior descending coronary artery were bypassed with a sequential saphenous vein graft.

After uneventful recovery, angiography was performed 1 month postoperatively. Although the other two grafts were widely patent, the GEA seemed to be a string (Figs 1A, 1B). After nitroglycerin injection from a catheter located at the orifice of the gastroduodenal artery, the GEA enlarged (Fig 1C).

Although catheter or guidewire stimulation was thought to be a cause of spasm, I have not experienced such a vigorous spasm in angiograms of the internal mammary artery. Therefore, I agree with the opinion of Mills and Everson that the GEA is prone to vasospasm. As a matter of fact, I have frequently observed surprisingly high free flow in the GEA after intraluminal papaverine injection at the time of operation even though its free flow was disappointingly low before papaverine injection. Mills and Bringaze [2] have described the efficacy of intraoperative intraluminal papaverine injection for the internal mammary artery graft; this method is extremely useful for the GEA graft also. I routinely have used it.

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Repair of Ductus Diverticulum Aneurysm

To the Editor:

I congratulate Baisden and co-workers [1] on the repair of a ductus diverticulum aneurysm using hypothermic circulatory arrest. They note in their report that their particular patient represented the 27th reported case of such an aneurysm repaired in an adult, and I would like to add the 28th.

In 1987 a 52-year-old man was noted to have an abnormality on his chest roentgenogram. Work-up revealed the ductus diverticulum aneurysm. Repair of the aneurysm was done using a median sternotomy and hypothermic circulatory arrest and a patch repair of the aneurysm using Dacron. We were fortunate that the phrenic and recurrent laryngeal nerves were not injured and the patient made a good recovery.

Repair of this type of aneurysm is easily accomplished with hypothermic circulatory arrest. Our experience would reinforce that of Baisden and co-workers using this beneficial technique in select cases.

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Reference

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Importance of Precordial Electrocardiogram Monitoring During Coronary Artery Bypass Grafting

To the Editor:

Routine precordial electrocardiogram (ECG) monitoring during coronary artery bypass grafting simultaneously with use of standard leads helps early detection of anterior myocardial injury. Until recently we used to monitor only standard ECG leads during coronary artery bypass grafting. This gives information only about the inferior wall of the myocardium.

For early detection and treatment of anterior injury we now monitor one precordial ECG lead during the bypass procedure. The patient is placed on the table with routine monitoring lines. After anesthesia, preparation, and draping, one precordial sterile ECG pad with electrode is placed over left anterior chest wall and connected to the ECG monitor together with standard leads. This precordial ECG lead stays under the V-drape or towel. Precordial ECG monitoring during coronary artery bypass grafting gives valuable information about the anterior part of the myocardium.

It is easy to apply and keep in place, and the only requirements are a sterile ECG pad and the lead. Simultaneous monitoring of standard leads and precordial lead covers the anterior and posterior walls of the myocardium. It helps early detection of compromised anterior myocardium and treatment while the patient is still on the operating table, and prevents late diagnosis of anterior wall injury in the cardiovascular intensive care unit.

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Resection of Atriocaval Adrenal Carcinoma

To the Editor:

I read the case report by Shahian and associates [1] with interest because my colleagues and I have had some experience with technique of resection of atriocaval adrenal carcinoma using hypothermic circulatory arrest [2].

Shahian and associates correctly emphasize the safety and excellent surgical exposure when one employs the technique of profound hypothermia and circulatory arrest. In addition, we have been impressed with the smooth postoperative convalescence and tumor-free survival that is exhibited by patients undergoing this procedure.

Shahian and associates may be interested to note that we previously reported resection of an adrenocortical carcinoma in a 1½-year-old child using the same surgical principles [3]. This patient had no tumor recurrence on early follow-up.

In my opinion, cardiothoracic surgeons owe a debt of gratitude to Drs Reitz and Marshall for their pioneering articles that so clearly elucidated the indications and technique for employing profound hypothermia and circulatory arrest [4, 5].

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Valvular Xenograft to Bioprosthesis

To the Editor:

I enjoyed the September supplement to *The Annals*, as well as participation in the program that produced the papers contained therein. I give congratulations to the editors and organizers of a very special meeting.

In the interest of historical accuracy I must correct an item in Alain Carpentier's paper [1]. I was no longer at Edwards Laboratories when he visited in 1968, having already started Hancock Laboratories. Animal implants were underway by that time and I did not have the opportunity of meeting Alain until some 2 years later at a lecture that he presented at Mt. Sinai Hospital in New York City, hosted by Bob Litwak. Our first formalin-fixed valve was implanted clinically in October 1968. Following experimental work our first glutaraldehyde-fixed valves were clinically implanted in April 1970.

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Reference

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Twenty-fifth Anniversary Meeting
The Society of Thoracic Surgeons

The Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons was held at the Baltimore Convention Center, September 11–13, 1989, with an attendance of 2,330 registrants, including spouses and exhibitors. The Scientific Sessions were attended by 708 members and 447 guests, including 125 residents. Five hundred seventy-one registrants were present at the Twenty-third Annual Postgraduate Course. At the Postgraduate luncheon, Dr John D. Minna spoke on "Oncogenes in the Pathogenesis of Lung Cancer." Co-Chairmen Drs Adnan Cobanoglu and Joseph I. Miller and the members of the Committee on Postgraduate Education are to be commended for putting together an excellent program.

Breakfast Sessions were held on two mornings. Attendance at each was limited to ensure informality and encourage member participation. The first Breakfast Session was devoted to case presentations of difficult problems and the second to small clinical workshops on selected topics. The success of these sessions and the scientific program was due chiefly to the substantial effort of the Program Committee under the vigorous leadership of Drs Fred A. Crawford, Jr, and Gordon F. Murray.

George G. Lindesmith's Presidential Address was entitled "Philosophy 1." It appears in this issue of *The Annals*. The J. Maxwell Chamberlain Memorial Paper, "Wound Complications After Coronary Bypass Surgery With Vein Grafts Only, One Internal Thoracic Artery Graft, or Two Internal Thoracic Artery Grafts," was presented by Dr Floyd D. Loop. His co-authors were Bruce W. Lytle, Delos M. Cosgrove III, Saade Mahfood, Marlene Goormastic, Robert W. Stewart, Leonard A. R. Golding, and Paul C. Taylor.

Dr Vincent L. Gott chaired the Local Arrangements Committee. Iveagh Gott headed the Spouses Hospitality Committee. Mrs Gott and all spouses serving on the committee provided an array of excellent tours and a warm and gracious spouses' hospitality area. The Annual Reception was attended by 732 members and guests at the National Aquarium and Lady Baltimore Showboat. Entertainment was provided by the Charlie Byrd Jazz Trio, in combination with the Annapolis Brass Quintet. Dr and Mrs Gott and their committees are to be commended for an outstanding effort to ensure the smoothly run program.

The Sixth Spouses Postgraduate Program was organized by Betsey Urschel. The attendance at this innovative program, "Growing Young: A Seminar on Innovative Approaches to the Process of Aging," was 52.

At the Annual Business Meeting, the following officers were elected: W. Gerald Rainer, *President*; Robert W. Jamplis, *Vice President*; Richard P. Anderson, *Secretary*; Robert L. Replogle, *Treasurer*; and Robert G. Ellison, *Historian*; Robert J. Ginsberg and Bill Nelems were elected *Councillors at Large*. Thomas B. Ferguson continues as *Editor* of *The Annals of Thoracic Surgery*. A complete list of the officers, committee members, and society representatives follows this report. The Society extends its appreciation to retiring officers and committee members for their dedicated service.

Ninety-four members were elected. These new members increased the total membership to 2,817.

The Smith Bucklin staff are to be commended for their hard work and diligence, which produced an outstanding meeting.

The next meeting of The Society will be an Interim Meeting in Chicago, Illinois, on September 21–23, 1990. The Twenty-sixth Annual Meeting will be held February 18–20, 1991, in San Francisco, California.

Richard P. Anderson, MD
Secretary

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Twentieth Congress of the Pan-Pacific Surgical Association, Kona, Hawaii—February 11–16, 1990

For information on this meeting, contact Pan-Pacific Surgical Association, 733 Bishop St, Suite 1910, Honolulu, HI 96813.

Nineteenth Annual Meeting of the German Society for Thoracic, Cardiac, and Vascular Surgery, Bad Nauheim, Federal Republic of Germany—February 22–24, 1990

For information on this meeting, contact Hagen D. Schulte, MD, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University, Moorenstrasse 5, D-4000 Dusseldorf, Federal Republic of Germany.

Twenty-ninth Annual Waring-Durrance Chest Conference, Aspen, Colorado—March 7–10, 1990

This meeting is sponsored by the Colorado Trudeau Society and the American Lung Association of Colorado. For information on this meeting, contact American Lung Association of Colorado, 1600 Race St, Denver, CO 80206.

Loma Linda International Conference on Pediatric Heart Transplantation, Palm Desert, California—March 11–14, 1990

For information on this meeting, contact Leonard Bailey, MD, Loma Linda International Heart Institute, Loma Linda University Medical Center, Loma Linda, CA 92350; or telephone (800) INTL-HEART.

Thirty-ninth Annual Meeting of the American College of Cardiology, New Orleans, Louisiana—March 18–22, 1990

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone 1 (800) 253-4636.

Annual Meeting of the International Society for Heart Transplantation, Fort Lauderdale, Florida—April 4–6, 1990

For information on this meeting, contact International Society for Heart Transplantation, 435 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-0828.

Modern Trends in Cardiac and Thoracic Surgery and Reunion of the Mark IV Club, Bristol, England—April 5–6, 1990

The symposium on modern trends in cardiac and thoracic surgery will be followed on April 7 by a reunion of the Mark IV Club (past residents of Ronald Belsey). For information on either of these meetings, contact Mrs Margaret Vickers, Symposium Coordinator, Department of Thoracic Surgery, Frenchay Hospital, Bristol BS16 1LE, England; or telephone 0272 701212, extension 2466.

Thirty-sixth Annual Meeting of the American Society for Artificial Internal Organs, Washington, DC—April 24–27, 1990

For information on this meeting, contact ASAIO Registration, PO Box C, Boca Raton, FL 33429.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the

Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660.

Seventieth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada—May 7–9, 1990

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Third International Symposium on Echocardiography and Doppler in Cardiac Surgery, Vienna, Austria—May 9–12, 1990

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450 Vienna, Austria; or telephone +43/1/23 69/2642 (telex: 11 18 03; facsimile: +43/1/23 69/648).

Eleventh Annual Scientific Session of the North American Society of Pacing and Electrophysiology, San Diego, California—May 31–June 2, 1990

For information on this meeting, contact the North American Society of Pacing and Electrophysiology, 13 Eaton Court, Wellesley Hills, MA 02181; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

Eighth Annual Uniformed Services University of Health Sciences Cardiothoracic Surgery Symposium, Washington, DC—May 31–June 2, 1990

For information on this meeting, contact Fred H. Edwards, MD, Department of Thoracic Surgery, Walter Reed Army Medical Center, Washington, DC 20307-5001; or telephone (202) 576-1433.

The Society for Vascular Surgery/International Society for Cardiovascular Surgery, Los Angeles, California—June 4–6, 1990

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Seventh International Congress Cardiostim 90, Nice, France—June 20–23, 1990

Cardiostim gathers several scientific events: Cardiostimulation 90 (cardiac pacing, electrophysiology, defibrillation), International Conference on High-Resolution ECG and Late Potentials, Fifth World Congress on Catheter Ablation, Cardio-Pharmaco 90, and Cardio-Rythmo 90. For information on this meeting, contact Secretariat Cardiostim 90, Department of Cardiac Pacing, Centre Chirurgical Val D'Or, 16, rue Pasteur, 92211 St. Cloud Cedex, France; or telephone (1) 46.02.70.72 (facsimile: (1) 46.02.05.09).

Sixteenth Annual Meeting of The Western Thoracic Surgical Association, Coronado, California—June 20–24, 1990

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Internal Thoracic Artery for Myocardial Revascularization, Toulouse, France—June 27–29, 1990

For information on this meeting, contact the Secretary of the Symposium, Department of Cardiovascular Surgery, Rangueil University Hospital, 31054 Toulouse Cedex, France; or telephone 61.32.26.51 or 61.32.26.53 (telex: 530 826 F).

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

Thirty-ninth Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary—September 9–12, 1990

For information on this meeting, contact Budapest Convention Centre, H-1444, PO Box 233, Budapest XI, Jagello u 1-3, Hungary; or telephone (361) 852-507 (facsimile: (361) 665-636; telex: 22-7717).

Interim Meeting of The Society of Thoracic Surgeons, Chicago, Illinois—September 22–23, 1990

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 440 Park Avenue South, New York, NY 10016 (telephone: (212) 684-5540; facsimile: (212) 545-0651). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $15.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3695). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

Please respond to Box 102. 102G/C

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

Please respond to Box 105. 105C/B

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

Please respond to Box 144. 144E/D

Cardiothoracic/vascular surgeon wanted to join established practice in Ohio. Recent graduate preferred. Please submit curriculum vitae and three references.

Please respond to Box 172. 172G/A

Cardiothoracic surgeon wanted for a busy, expanding, 3-man, private practice group in the Midwest. Applicant must be ABTS eligible or certified. Prefer recent graduate with some background in electrophysiologic surgery. Please send curriculum vitae.

Please respond to Box 189. 189H/G

Cardiovascular and thoracic surgeon wanted to join busy practice in Fort Lauderdale, Florida. Recent US medical graduate preferred.

Please send CV to I. Tabry, MD, 2773 NE 37th Drive, Fort Lauderdale, FL 33308. (Telephone: (305) 561-9781 after 9:00 PM.) 208J/C

Cardiothoracic surgeon, BE/BC, to join expanding practice of cardiac/thoracic surgery at 719-bed hospital (Rhode Island Hospital) and major affiliate of medical school. Excellent clinical and investigational facilities available with ample opportunities for clinical or basic science research. Private practice with academic affiliation, solid general surgical residency with active medical student participation. Salaried position leading to eventual partnership for right individual.

Send curriculum vitae to Arun K. Singh, MD, 110 Lockwood St, Providence, RI 02903; (401) 274-7546. 217K/A

Cardiothoracic/vascular surgeon, BE/BC, with primary interest in cardiac surgery, wanted immediately to replace member of established 6-physician surgical group practicing in Allentown, PA. Competitive salary/fringe benefits. Position leads to partnership for successful candidate. Please respond with CV, history of clinical experience, references, and salary requirements.

Please respond to Box 218. 218K/D

Cardiothoracic surgeon: Exceptional opportunity for an additional cardiothoracic surgeon to join an established, multispecialty group practice in the Tampa Bay area. Recent graduate preferred. Must be experienced in all areas of adult cardiac, thoracic, and peripheral vascular surgery. Training in valve repair, electrophysiologic surgery, and left ventricular assist devices desirable. Guaranteed first year salary leading to potential directorship.

For immediate consideration, rush CV in confidence c/o Recruitment Committee: Diagnostic Clinic, PO Box 2901, Largo, FL 34649. 219K/A

Cardiovascular surgeon wanted to join busy private practice in excellent Florida location. Practice includes all aspects of adult cardiovascular and thoracic surgery. Would prefer a recent graduate. Send curriculum vitae.

Please respond to Box 223. 223K/A

Cardiothoracic surgeon wanted—to join established cardiac and thoracic surgeon in the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Please send curriculum vitae.

Please respond to Box 225. 225K/A

Cardiac-thoracic surgeon, needed for expanding program on west coast of Florida. Excellent opportunity, private practice, primarily adult cardiac including cardiac transplantation. BC/BE required. Please send CV.

Please respond to Box 226. 226K/D

Thoracic surgery residency: Newly approved residency in thoracic surgery to begin July 1990 at the University of Massachusetts Medical School/Hospital. Three-year program includes training in adult and pediatric cardiac and general thoracic surgery.

Interested candidates may contact Thomas J. Vander Salm, MD, Department of Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655. 228K/A

Cardiothoracic surgeon, BE/BC, wanted to join surgeon in active cardiac/thoracic/vascular surgical practice in northern Alabama community of 80,000 (300,000 population draw). Clinical practice in two community hospitals. Lake/mountain recreation facilities. Generous compensation, future partnership.

Please write Sara Fleming, Business Manager, 801 Gaines Ave, Suite 305, Gadsden, AL 35903; (205) 492-9360. 237L/E

Cardiothoracic surgeon wanted to join established practice in Long Island, NY, area. Recent graduate preferred. Please submit curriculum vitae and references.

Please respond to Box 238. 238L/B

Associate Director for Heart Transplantation is urgently needed for rapidly expanding heart transplantation program in California.

Please respond with curriculum vitae to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 240L/K

Assistant surgeon—experienced in cardiothoracic surgery to first assist in the operating room. Active adult and pediatric cardiovascular surgery practice in southern California.

Please respond with curriculum vitae and outline of surgical experience to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 241L/K

Cardiothoracic and vascular surgeon, BC/BE, recent graduate to join private practice of adult cardiac, pulmonary, and vascular surgery located in New Jersey. Please submit curriculum vitae.

Please respond to Box 243. 243L/C

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 244L/A

Thoracic and cardiovascular surgeon, board eligible or board certified, wanted for an established, busy 2-man practice in Northeast. Must be familiar with all aspects of adult cardiac, thoracic, and peripheral vascular surgery including experience or training in laser-assisted balloon angioplasty. Salaried position leading to partnership. Submit curriculum vitae and references.

Please respond to Box 245. 245L/A

Cardiac surgeon, board certified or eligible, needed for a growing cardiac surgery program in the Southeast. Excellent opportunity for someone primarily interested in adult cardiac surgery.

Please respond to Box 248. 248L/B

Thoracic surgeon. A 230-physician multispecialty prepaid group in Hawaii is seeking a qualified MD to accept the second thoracic surgery position. Must be experienced in adult cardiac, general thoracic, and peripheral vascular surgery. Excellent fringe benefits. Malpractice paid.

Please direct curiculum vitae to Hawaii Permanente Medical Group, Inc, 3288 Moanalua Rd, Honolulu, HI 96819. An equal opportunity employer. 250L/B

Cardiovascular and thoracic surgeon, board eligible/certified, wanted to join expanding 2-man private practice located in Ft. Lauderdale, FL. Send CV.

Please respond to Box 251. 251L/E

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to Box 252. 252L/F

Thoracic-vascular surgeon wanted to join busy practice in Northeast. Board certified or eligible. Interested in practice of vascular and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 254. 254L/F

Cardiothoracic and vascular surgeon wanted to be first assistant. Twenty years experience preferred. Interested in practice of cardiac, vascular, and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 255. 255L/F

Cardiothoracic surgeon—to join a 2-man private practice in cardiac, thoracic, and vascular surgery in the Great Lakes region. Must be board certified or eligible. Recent graduates considered. Send curriculum vitae.

Please respond to Box 260. 260L/A

Cardiovascular/thoracic surgeon, board certified or eligible, wanted to join busy private practice in the Midwest in adult cardiac, thoracic, and vascular surgery. Initial contact should include curriculum vitae, clinical experience, and names of references.

Please respond to Box 265. 265L/A

Thoracic-vascular surgeon: Excellent opportunity for a board-certified or board-eligible noncardiac thoracic-vascular surgeon to join group practice on south shore of Long Island. Associated with two large level II 400-bed hospitals, fine recreational facilities, including beaches and boating, quality schools, and excellent homes.

Please respond to Box 148. 148EGIKA

Cardiothoracic surgeon, experienced in cardiac arrhythmia surgery, to join well-established cardiac surgical group in central Florida. Send CV.

Please respond to Box 267. 267A/L

Cardiovascular and thoracic surgeon, BE/BC, to join established private practice in San Francisco Bay area. Practice includes adult cardiac, thoracic, and vascular surgery. Initial contact should include curriculum vitae and references.

Please respond to Box 268. 268A/C

Cardiothoracic surgeon: Private practice position, Great Lakes, adult cardiothoracic and vascular surgery. Must be currently active in cardiac surgery. Send CV and references.

Please respond to Box 269. 269A/C

Cardiothoracic surgeon: The Oregon Health Sciences University, Division of Cardiopulmonary Surgery, with strong active programs in all aspects of cardiopulmonary surgery and heart transplantation, has an academic position available at the Assistant Professor level. Candidates should be eligible for or certified by the American Board of Thoracic Surgery. Outstanding opportunity for an individual with excellent clinical skills, a track record of academic productivity, and a commitment to research and teaching. Two to 4 years of postresidency clinical experience is highly desirable.

Applicants are invited to respond with curriculum vitae to Adnan Cobanoglu, MD, Professor and Chief, Division of Cardiopulmonary Surgery, The Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201. 270AB

Cardiac surgeon: Seeking board certified cardiac surgeon with proven track record to develop new open heart program in a western Pennsylvania community, teaching hospital. Initial response should include CV, clinical experience, and references.

All correspondence should be directed to Kenneth Rowe, MD, Senior Vice President, Medical Affairs. Conemaugh Valley Memorial Hospital, Johnstown, PA 15905. 272A

Chairperson, Department of Thoracic-Cardiovascular Surgery. Winthrop-University Hospital, a 533-bed tertiary care hospital of SUNY Stony Brook, is seeking candidates to chair its cardiothoracic department. Applicants should have strong clinical, teaching, and administrative skills, as well as a commitment to research. The department conducts a fully approved open heart program and performs a large volume of thoracic and vascular surgery. The hospital will support a fellowship program and research activities.

Send CV to Alan Fein, MD, Chairman, TCV Search Committee, Winthrop-University Hospital, c/o 222 Station Plaza No., Suite 400, Mineola, NY 11501. 273A/C

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland OR 97213-2282. 274A/F

Cardiovascular and thoracic surgeon: Position available for a board certified or board eligible to join practice in Northeast involved in adult cardiac, thoracic, and vascular surgery. Association will lead to partnership. Excellent fringe benefits. Please send curriculum vitae.

Please respond to Box 275. 275A/F

Cardiothoracic transplant surgeon, board certified or eligible, wanted to join established practice. Experience required in transplantation, adult cardiac surgery, and thoracic surgery. Northwest city with easy lifestyle and outdoor activities. Salary leading to partnership.

Please respond to Box 276. 276A/C

Cardiac surgeon, board eligible/certified, with at least 2 years experience in adult cardiac surgery, wanted to join well-established 2-surgeon practice located in south Florida.

Please respond to Box 277. 277A/C

The Department of Surgery, University of California, San Francisco, is seeking a chief of cardiothoracic surgery, with expertise in surgery of adults and infants, to lead the cardiothoracic program at UCSF and its affiliated hospitals. Individuals must have solid research background in related areas and be board certified in general and thoracic surgery. The candidate will assume appropriate administrative and teaching responsibilities and must have excellent command of his/her subject, have ability to organize and present material in a logical and stimulating fashion, participate in general guidance and advising of students and residents, and show continuous growth in the field of cardiothoracic surgery. Candidate must be effectively engaged in creative research of the highest quality and significance, with particular interest in circulation and myocardial physiology, and will be expected to actively participate in patient care, help with coverage of cardiothoracic surgery clinic, make daily ward rounds with house staff, and attend and participate in Grand Rounds and Death and Complications meeting each Saturday that they are held, and will at all times be concerned with the care and treatment of patients. The candidate should be willing to serve on various committees within the Medical Center, and should be willing to lecture in other institutions when asked, as well as participate in courses given under the auspices of extramural educational or scientific groups.

Candidates should send curriculum vitae to Lawrence W. Way, MD, Professor and Vice-Chair, Department of Surgery, and Chief of the Surgical Service, Veterans Administration Medical Center (112), 4150 Clement St, San Francisco, CA 94121. The University of California, San Francisco, is an affirmative action/equal opportunity employer. 279A

SITUATIONS WANTED

Cardiothoracic and vascular surgeon, American, 32, board-eligible finishing June 1990. In active major midwestern training program. Experienced in adult coronary and valvular surgery, pediatric cardiac surgery, reoperations, internal mammary artery surgery, electrophysiology and aortic surgery, and heart transplantation/assist devices. Seeks practice in Northeast/Midwest. Curriculum vitae and references upon request.

Please respond to Box 239. 239L/A

Cardiothoracic surgeon, 33, American, university trained, wishes to relocate. ABS, BE for ABTS. Experience in IMA and AICD surgery. Seeks position in private practice or academics. Curriculum vitae and references upon request.

Please respond to Box 262. 262L/B

Cardiovascular and thoracic surgeon, 45, ABS, ABTS, seeks relocation. Twelve years private practice and university experience.

Please respond to Box 271. 271A/C

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 222K/D

Cardiopulmonary surgery fellow: Immediate opening of a clinical position for 1 year in a busy university service that performs adult cardiac surgery, thoracic surgery, pediatric heart surgery, and cardiac transplantation. The Fellow will be given responsibilities in perioperative care and as assistant and operating surgeon based on prior experience. Ideal position for a senior surgical resident who would like to attain additional experience in cardiopulmonary surgery or a resident waiting to enter a thoracic surgery residency.

Please respond with curriculum vitae to Adnan Cobanoglu, MD, The Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201. 242L/B

Fellowship in pediatric cardiovascular surgery available July 1990. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40's.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453; or telephone (312) 857-3029. 253L/D

Fellowship in adult cardiac surgery available for 1 or 2 years in private program performing over 600 open heart procedures yearly. General surgery training required. ECFMG and visa qualified foreign applicants accepted.

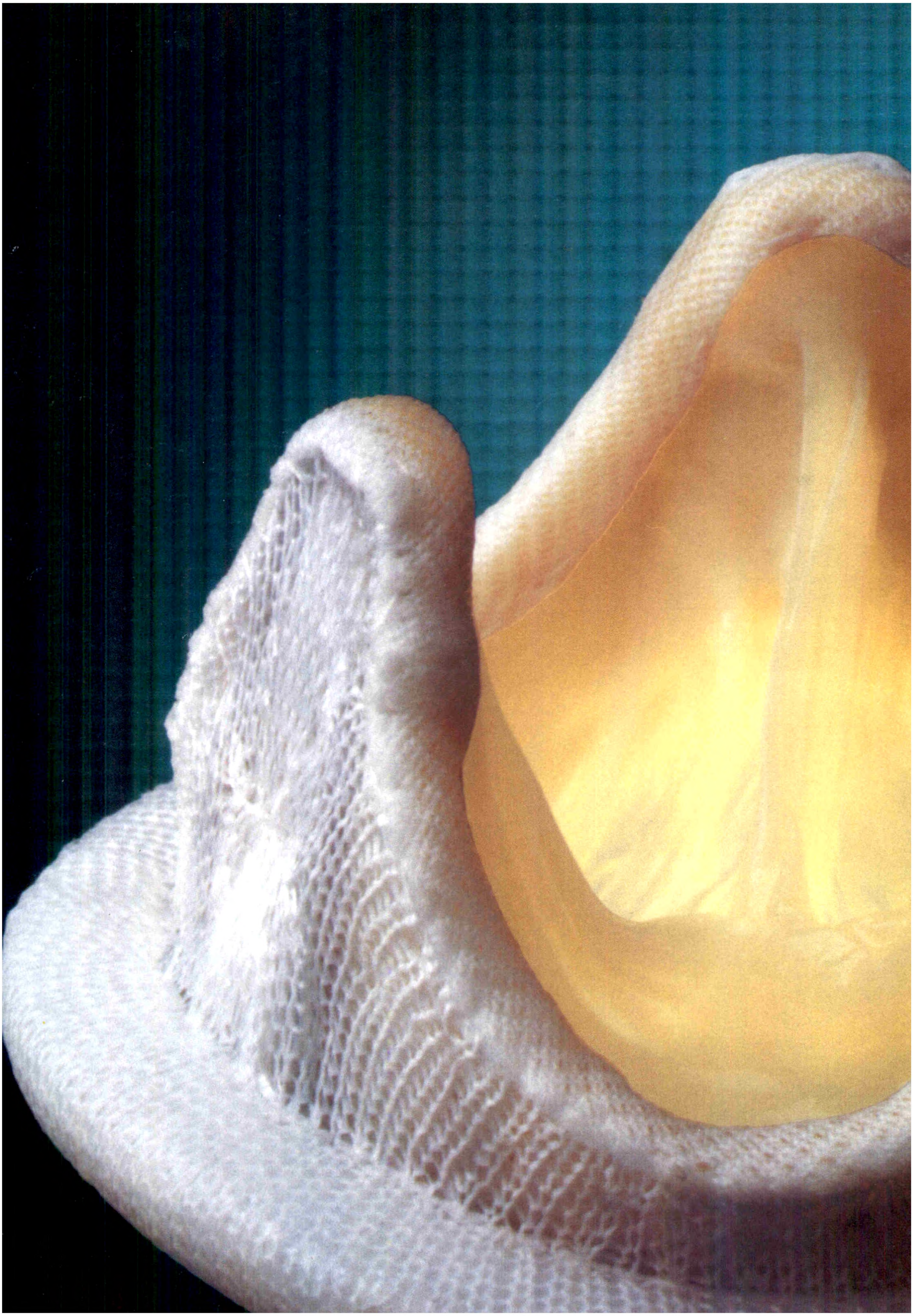
Send curriculum vitae to Donald R. Kahn, MD, 817 Princeton Ave, Suite 300, Birmingham, AL 35211. 263L/B

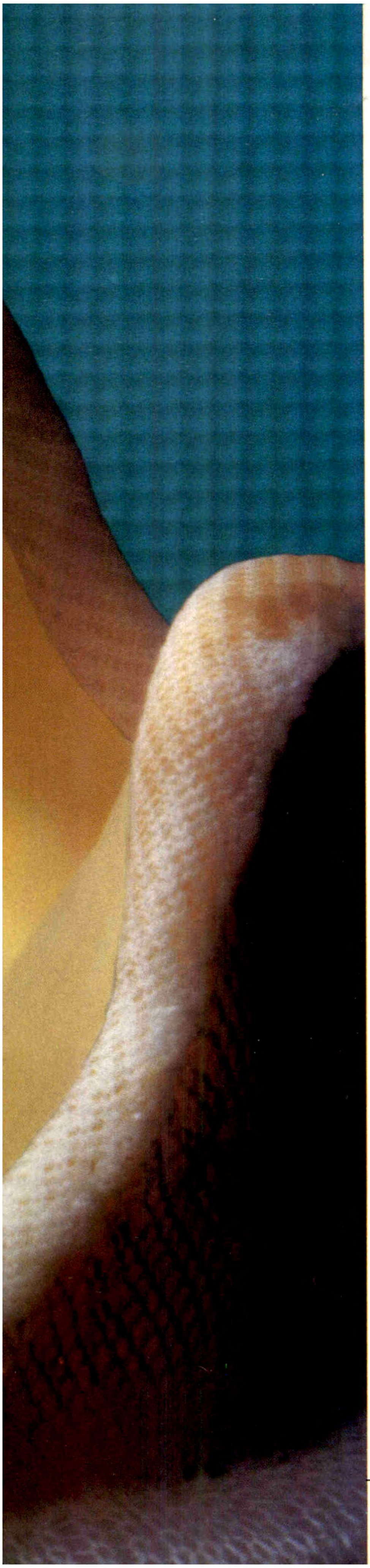
Research fellowship: a 2-year cardiovascular research fellowship is available in the laboratory at New York University Medical Center beginning July 1, 1990.

Respond with CV to Aubrey C. Galloway, MD, NYU Medical Center, 530 First Ave, Suite 6D, New York, NY 10016. 266A

Surgical fellow: Clinical fellowship position available in adult cardiothoracic surgery. Large volume of cases. NJ license required. Excellent salary and benefits.

Send curriculum vitae to Bruce P. Mindich, MD, Director, Cardiovascular Surgery, The Valley Hospital, 223 N Van Dien Ave, Ridgewood, NJ 07450. 278A





In over 270,000 cases, physicians chose one tissue heart valve over any other.

Our long-term commitment to engineering and design has resulted in today's number one choice in tissue valves. The Carpentier-Edwards® Bioprosthesis benefits from the flexibility of our unique Elgiloy* stent and our advanced tissue preservation techniques. The result is a tissue valve of improved hemodynamics and excellent durability.

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Indications: Bioprostheses are indicated for use in patients suffering from valvular heart disease. Aortic and mitral valvular heart disease are conditions involving any of the following: obstructions of the heart valves, or stenosis; leakage of the valves, known as regurgitation or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions. Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia. Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy. The Carpentier-Edwards bioprosthesis is intended for use in patients whose aortic or mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic or mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis. **Warnings:** For Single Patient Use Only In the presence of conditions affecting calcium metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, in the presence of severe systemic hypertension, and in patients who are on maintenance hemodialysis. The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must **not** be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. 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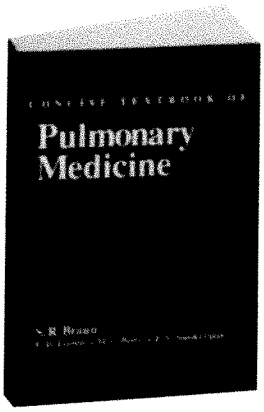

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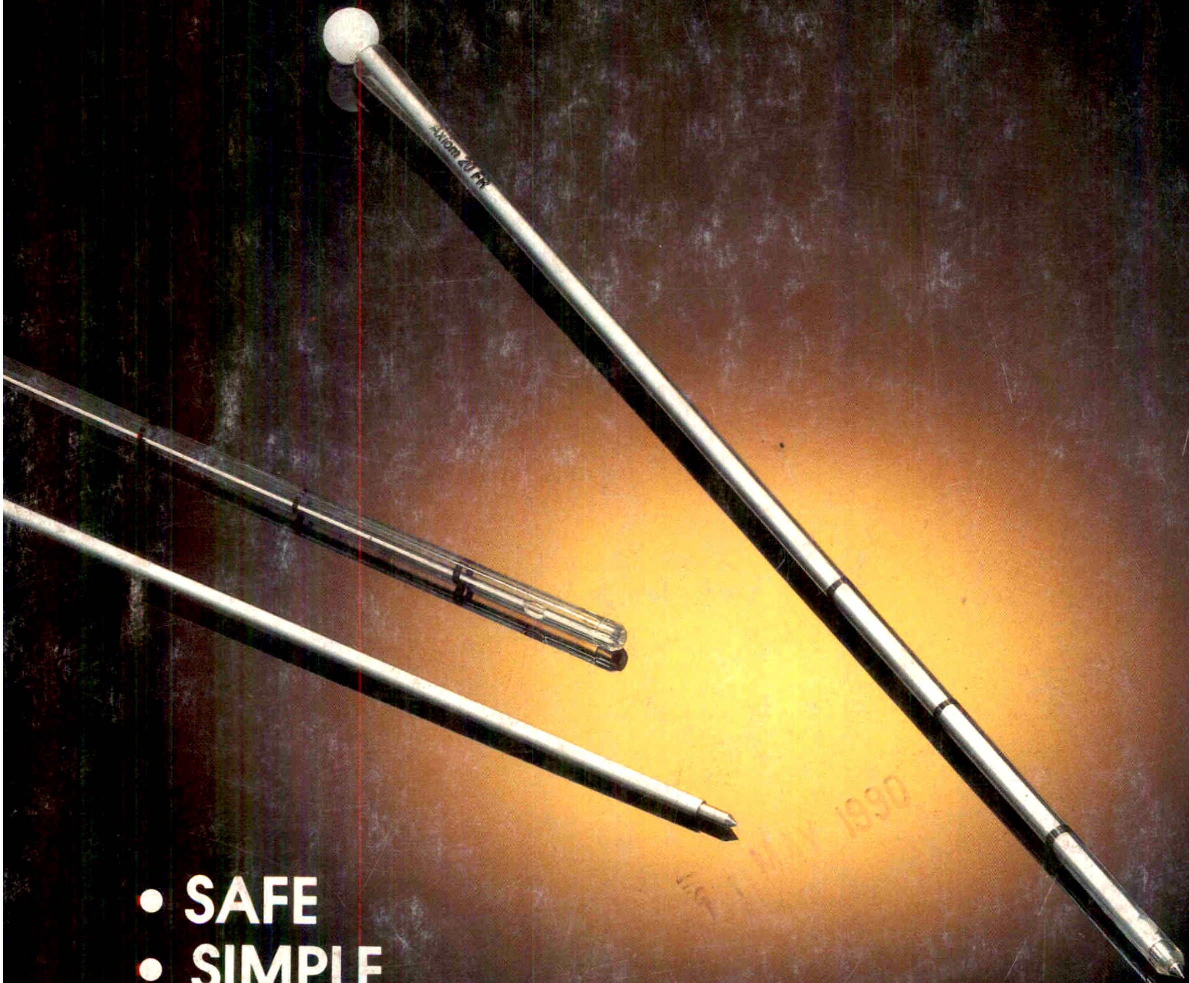

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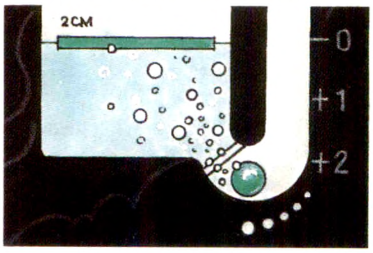

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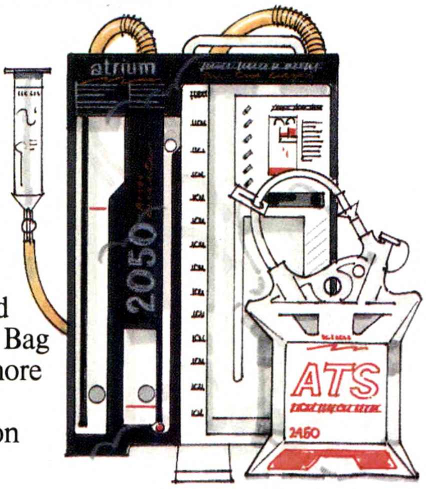

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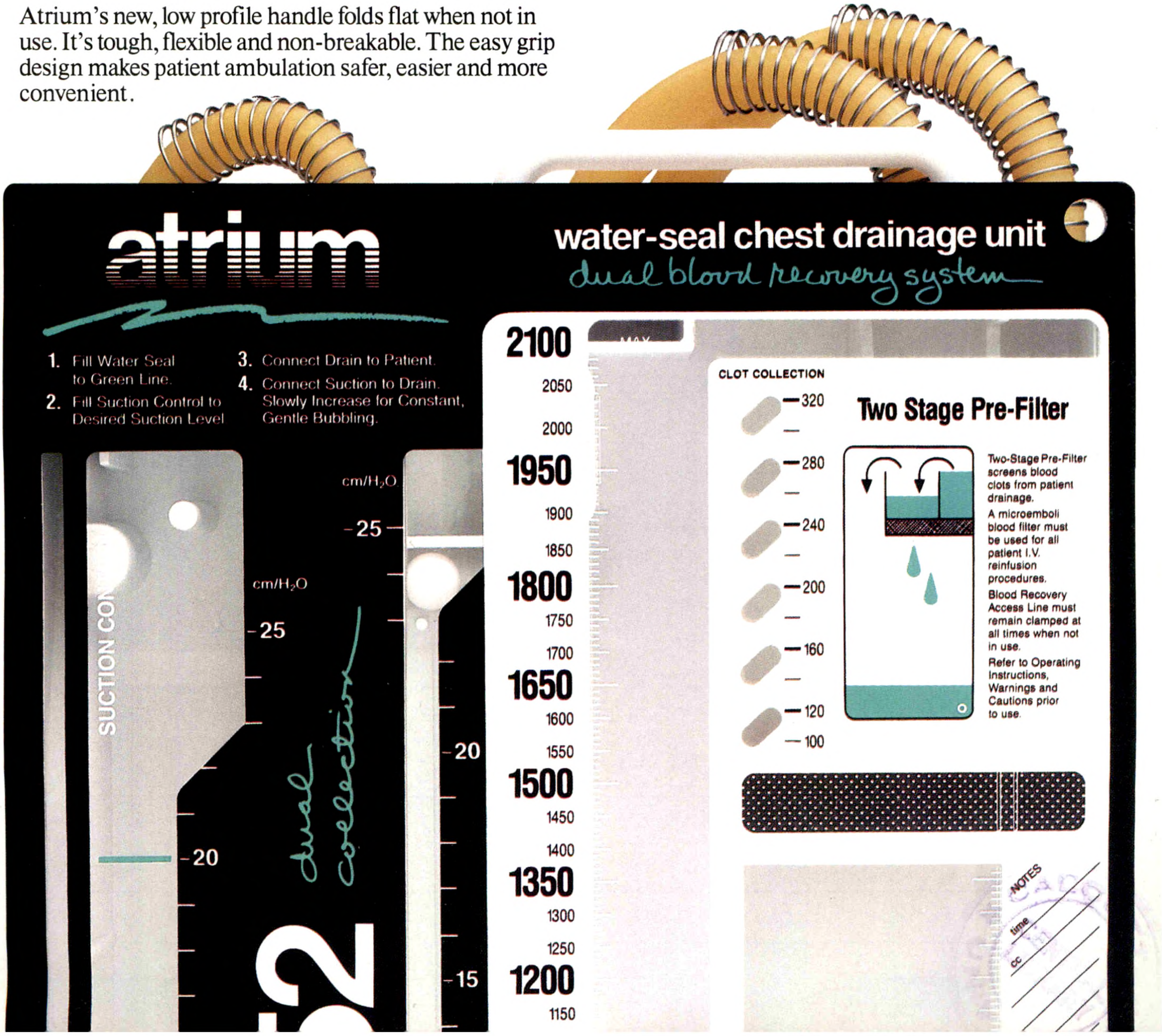

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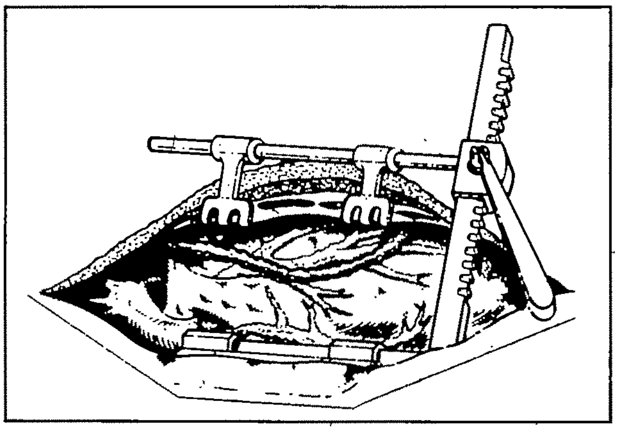

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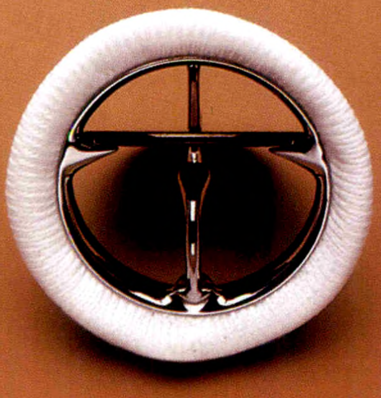

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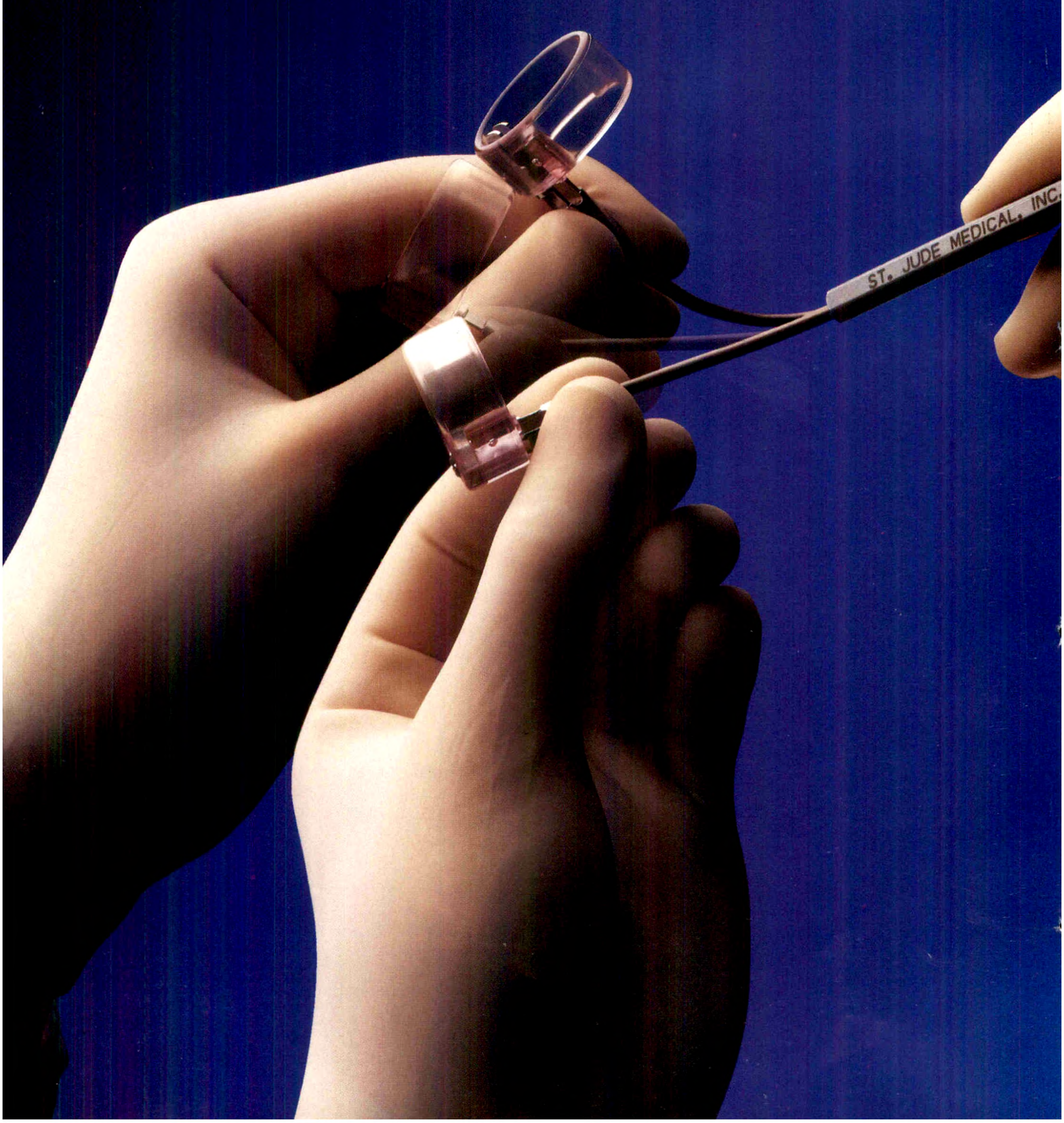

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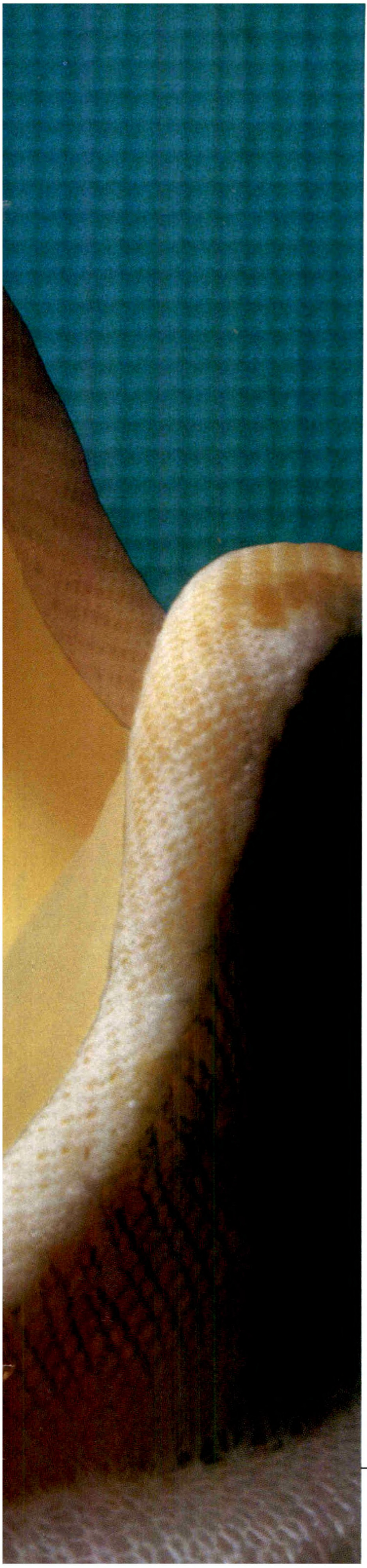

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The Carpentier-Edwards bioprosthesis is intended for use in patients whose aortic or mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic or mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis. **Warnings:** For Single Patient Use Only In the presence of conditions affecting calcium metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, in the presence of severe systemic hypertension, and in patients who are on maintenance hemodialysis. The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must **not** be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards bioprostheses to calcification as compared to other commercially available porcine valves. **Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician. Baxter International Inc. is the owner of the following US patent which covers the products described herein: 4,106,129. Patent numbers in foreign countries supplied upon request. See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information. Carpentier-Edwards® is a registered trademark of Baxter International Inc.

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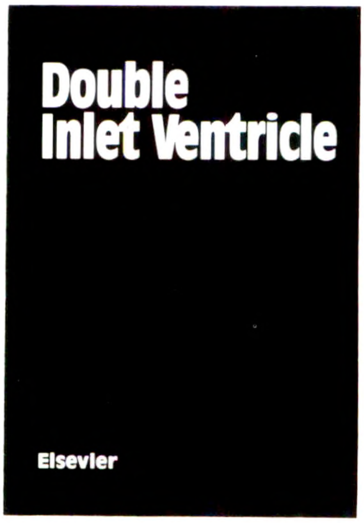
A complete and concise review



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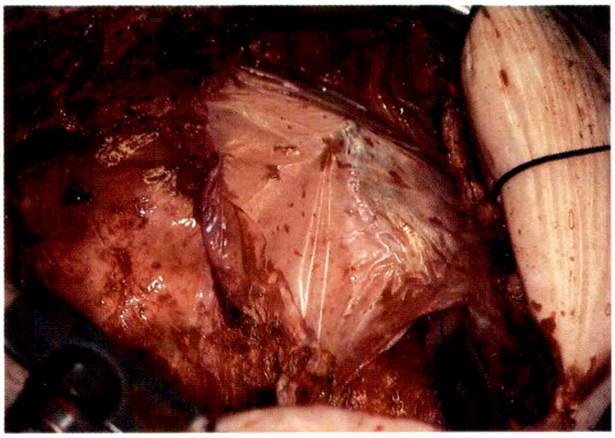

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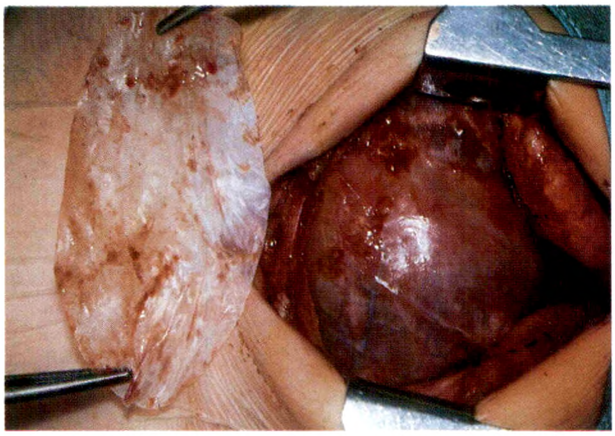

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Chapter in Book

12. Katz PO. Achalasia. In: Castell DO, Richter JE, Dalton CB, eds. Esophageal motility testing. New York: Elsevier Science Publishing Company, 1987:107.

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Getting the Most Mileage From Donated Hearts

Paul Terasaki, PhD

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In their article in this issue, DiSesa and his colleagues [1] of Boston's Brigham and Women's Hospital suggest that human lymphocyte antigen (HLA) matching may be a reasonable method of allocation of hearts for transplantation. Although probably no areas in the United States currently allocate hearts in this way (and surgeons may be loath to do so), there are several valid reasons for considering HLA matching.

The influence of HLA matching on the outcome of kidney transplantation, especially in the long term, has already been shown. Heart transplants are subject to the same incompatibility reaction as kidneys, particularly with respect to long-term survival. As noted in the Stanford experience, the 5-year survival rate of random donor heart transplants, even with cyclosporine, was 53% [2] compared with 47% with kidney transplants [3]. Thus, incompatible transplants fail at the same rate in both these types of transplantation. With HLA matching, the kidney graft survival at 3 years was 73% for transplants with zero BDR mismatches compared with 56% for transplants with 4 BDR mismatches [4].

The importance of HLA matching in heart transplants has been demonstrated, although admittedly in much smaller numbers and with less significance. DiSesa and associates analyzed 51 transplants retrospectively for correlation of HLA-AB locus matching with outcome and found that even though deaths were not significantly correlated with mismatching, incidences of rejection episodes were reduced in patients with lower mismatch grades.

See also page 220.

The Yacoub group [5] published a much larger series (which was not cited by DiSesa and associates) in which the 2-year survival was 84% for patients with 1 DR mismatch compared with 68% for patients with 2 DR mismatches. The effect of DR antigens was more significant than that of AB locus products.

An even larger series consisting of 179 patients with longer follow-up (also not cited) was published by the Stanford group, Frist and co-workers [6]. Patients with 0 or 1 mismatch at the AB locus had a 4-year survival rate of 88% compared with 54% for those with 4 antigens of mismatch. Frist and co-workers demonstrated that the effect of mismatching increases with time, as noted in kidney transplants. The infection rate was lower in the well-matched transplants, probably reflecting the need for less immunosuppression in compatible recipients.

Because these series were analyses of randomly performed transplantations, only a few transplantations of exceptionally well-matched hearts were performed. Thus, critical information on zero-mismatched heart transplant patients is still lacking. In contrast, many kidney transplantations were achieved by shipping kidneys to well-matched recipients in a large pool.

Through a United Network for Organ Sharing (UNOS) agreement, transplantation of 6-antigen-matched kidneys were performed during the past 2 years. As many as 400 such well-matched grafts were shipped from more than 100 centers to 100 other centers in the United States. In a preliminary analysis of 123 transplantations, 90% 1-year graft survival was noted for shipped 6-antigen-matched kidneys versus 79% in control nonshipped kidney grafts in incompatible patients [7].

Based on numerous studies, it is now very well established that HLA matching is important for retransplantation. As more patients receive cardiac transplants, the retransplantation rate will increase as it has for kidney transplantation. Therefore, it is important to have an HLA matching system to accommodate these patients.

There is no evidence that waiting time, often used as the main criteria for patient selection, has any influence on ultimate outcome. Waiting time should therefore be considered principally with regard to medical urgency. HLA matching and effective immunosuppression are factors associated with high survival rates.

Complications When Using HLA Typing for Transplant Recipient Selection

Because artificial hearts are not yet developed to the same level as artificial kidneys, large pools of prospective heart transplant patients cannot be maintained. This means that in many instances, a patient cannot wait for an ideally matched graft because medical urgency is often so acute that the next available heart must be used.

Because the polymorphism of HLA is so great, effective HLA matching can only be achieved with large pools of waiting patients and national shipping. This will necessitate not only better maintenance of artificial hearts but also better means of heart preservation for up to 48 hours. The University of Wisconsin solution (developed by Belzer and colleagues) has been proved very effective in liver preservation. Similar solutions will need to be devised for heart transplants.

Solutions

Dr Thomas Starzl [8] of the University of Pittsburgh has suggested a point system whereby points can be assigned to different factors to be used for patient selection. United Network for Organ Sharing already has a point system for

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kidney transplants that takes HLA matching into account. For implementation for heart transplants, only the introduction of HLA into the existing point system would be required. In the early phases, a relatively small fraction would need to be assigned to tissue typing; then as storage methods improve, the weight assigned to HLA could be increased proportionately.

The supply level of donor hearts must be increased substantially so that surgeons will be amenable to sharing hearts with other United States centers. With the current severe shortage, surgeons are understandably pressured to first meet their immediate local patient needs.

Much has been said recently about the selection system being "patient driven" rather than "physician or center driven." In other words, the heart should be given to the most "deserving" patient rather than to the patient who happens to be under the care of the surgeon who retrieves the organ. Although efforts should be expended to achieve this ideal situation, it should be noted that selection should also be "society driven." If the valuable organ is viewed as a donation to society in general, then this scarce, irreplaceable resource should be utilized in the manner that best ensures the longest probability of survival for that organ.

The question then becomes "who will be able to keep the heart for the longest period of time," rather than "who needs the heart most." If it were decided that this line of reasoning should be followed, then HLA matching would figure prominently in the equation.

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J. Maxwell Chamberlain Memorial Paper

Sternal Wound Complications After Isolated Coronary Artery Bypass Grafting: Early and Late Mortality, Morbidity, and Cost of Care

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Of 6,504 consecutive patients who underwent isolated coronary bypass grafting in 1985 to 1987, 72 (1.1%) patients experienced sternal wound complications. Ten patients (14%) with wound complications died of multisystem failure. Only the patients with negative cultures fared well; of the bacterial culture categories, polymicrobial infection carried the worst prognosis. Effects of recurring infection were seen throughout the first year. Patients, grouped according to conduits received, experienced these wound complication rates: vein grafts only, 11/1,085 (1.0%); one internal thoracic artery, 38/4,073 (0.9%); and bilateral internal thoracic artery grafts, 23/1,346 (1.7%). There were no significant differences in wound complication rates between primary and reoperation patients or among conduit groups. By logistic regression analysis, the relative risk for patients with diabetes and bilateral internal thoracic artery grafting was 5.00 (95% confidence interval, 2.4 to 10.5). Operation time as a continuous variable increased the relative risk of wound complication 1.47 times per hour (1.3 to 1.7); obesity, 2.90 times (1.8 to 4.8); and blood units as continuous variable, 1.05 times per unit (1.01 to 1.10). Bilateral internal thoracic artery grafting in nondiabetic patients carried no greater risk of wound complication than that in patients with vein grafts only or with one internal thoracic artery graft.

(Ann Thorac Surg 1990;49:179–87)

> If it be established that median thoracic incision is a fairly safe procedure, I have no doubt that it will constitute the most generally useful route to the thoracic organs. And if once a safe route is established, a great field for surgical interference lies open.
>
> H. Milton, MRCSEng
> Kasr El Aini Hospital, Cairo, 1897 [1]

In the face of the changing practice of coronary artery grafting, it is essential to continuously scrutinize the clinical risk factors for wound complications, as well as their implications for patient outcome, including mortality, morbidity, need for continued therapy, and effect on overall cost of care. Prevention and better treatment of sternal wound complications must be a major goal in assuring the highest quality of cardiovascular surgical care.

We studied wound complications in isolated coronary artery grafting patients from 1985 to 1987. During these years, wound infection rates for valve operations (4/1,110, 0.4%) and for coronary bypass grafting combined with other cardiac operations (9/870, 1.0%) were lower than that for isolated coronary bypass grafting. The more uniform, isolated coronary artery grafting cohort was chosen to eliminate additional variables introduced by other procedures and to identify factors responsible for mediastinitis, including the effect of bilateral internal thoracic artery grafting on sternal wound complication rates.

This consecutive, isolated coronary bypass series was selected for the following reasons: (1) established and unchanged surgical staff; (2) single hospital practice; (3) extensive experience in coronary artery grafting, including expanded use of internal thoracic artery grafting; (4) fixed protocol for skin preparation and draping; (5) identical antibiotic regimen used throughout the study; and (6) similar clinical outcomes among staff surgeons. The terms *wound complication*, *wound infection*, and *mediastinitis* are used interchangeably and signify a retrosternal process as opposed to a superficial infection confined to subcutaneous tissue.

Patients and Methods

We surveyed records of 6,504 consecutive patients who underwent isolated coronary artery bypass grafting from January 1, 1985, through December 31, 1987. A wound complication was defined as mediastinitis, dehiscence, or both. Data were retrieved through our Cardiovascular

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Table 1. Clinical, Angiographic, and Operative Variables Found in 6,504 Isolated Coronary Artery Bypass Patients Grouped by Type of Conduit (1985–1987)

Variable	Vein Grafts Only (n = 1085)	1 Internal Thoracic Artery (n = 4073)	2 Internal Thoracic Arteries (n = 1346)	*p* Value
Mean age (yr)[a]	65.6 (9.2)	61.6 (8.7)	54.9 (8.7)	<0.001
Male (%)	72.7	78.0	91.5	<0.001
Diabetes (%)	15.3	16.8	10.5	<0.001
Obesity (%)	13.7	19.1	20.0	<0.001
Hypertension	53.7	53.2	46.0	<0.001
Peripheral vascular atherosclerosis (%)	22.6	18.6	10.8	<0.001
Extent of disease (%)				
One-vessel	3.8	6.2	1.6	<0.001
Two-vessel	25.0	21.6	23.0	
Three-vessel	51.5	55.8	62.6	
Left main	19.7	16.4	12.9	
Left ventricular function (%)				
Normal	58.0	62.3	60.2	<0.001
Mild	17.6	20.7	24.0	
Moderate	13.6	11.6	11.0	
Severe	10.8	5.5	4.8	
Primary operation	63.8	85.5	89.1	
Reoperation	36.2	14.5	10.9	<0.001

[a] Numbers in parentheses are percentages.

Information Registry, a computerized data base in operation since 1971.

Clinical Findings

Among 5,369 primary (first time) coronary bypass patients, 55 (1.0%) experienced wound complications (15 women and 40 men). Their median age was 62 years. Of 1,135 patients who underwent reoperation, 17 (1.5%) had wound complications (three women and 14 men). Their median age was 59 years. Overall, 72 patients (1.1%) had sternal wound complications. All patients with wound complication were followed and none were lost to follow-up. To the best of our knowledge, all infected patients in these years were treated at the Cleveland Clinic. Information on hospital survivors was obtained by trained personnel by telephone or through records of local physicians, autopsy reports, or Cleveland Clinic outpatient or readmission chart review.

Patients were grouped by type of conduit used in grafting: (1) vein grafts only; (2) one internal thoracic artery graft, either alone or combined with vein grafts; and (3) bilateral internal thoracic artery grafts, either alone or combined with vein grafts. Clinical, angiographic, and operative variables pertaining to these conduit groups are shown in Table 1. The incidence of wound complications in these groups was further categorized by primary and reoperative cases as shown in Table 2. There were no significant differences in wound complication rates among the three conduit groups, between primary and reoperative cases, or by individual year surveyed. The mean interval between operation and diagnosis of wound complication was 11 days (range, two to 64 days). Concomitant fever and wound drainage was the most frequent sign of wound problems. Wound culture results were obtained for all patients. Bacteria or fungus, or both, was isolated in 61 patients. In those 61 patients, white blood cell counts before diagnosis of wound complication ranged from 4.5 to 32.5 × 10^9/L (mean, 13.56 × 10^9/L; median, 12.1 × 10^9/L). Sixteen (22%) patients were readmitted because of wound complication first manifested after initial discharge.

Table 2. Incidence of Wound Complications After Coronary Artery Bypass Grafting

Conduit Type	Primary (%)	Reoperation (%)
Vein grafts	6/690 (0.9)	5/395 (1.3)
One internal thoracic artery	30/3480 (0.9)	8/593 (1.3)
Bilateral internal thoracic arteries	19/1199 (1.6)	4/147 (2.7)
Total	55/5369 (1.0)	17/1135 (1.5)

Bacteriologic Findings

Eleven patients with negative cultures acquired sternal wound complication significantly earlier than patients with polymicrobial infections (Fig 1). Positive cultures were grouped into these categories: gram-positive cocci, gram-negative bacilli, gram-positive bacilli, and polymicrobial organisms. In these 61 patients with positive cultures, there were no appreciable differences in incubation periods.

Wound culture results were correlated with the conduit groups. *Staphylococcus* species (41 of 61 positive cultures) and Enterobacteriaceae (17 of 61) predominated. There

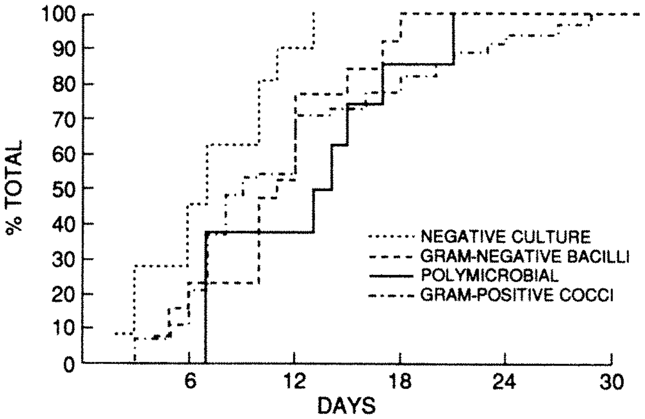

Fig 1. Onset of sternal wound complication expressed as interval in days after operation (after Bor and associates [17]). Patients with negative cultures were diagnosed significantly earlier (seven days) than patients with polymicrobial infections (13 days) (p = 0.005).

was no discernible difference in the distribution of organisms between the three conduit groups. Blood cultures were positive in 26 patients (36%): 13 before or at the time of discovery of wound complication and 13 after discovery.

Concomitant infections at other sites included pneumonia, 14 patients; urinary tract infection, 9; femoral incision, 6 (2 at site of intraaortic balloon pump); and leg incision, 1. Six patients had infections in one or more of these sites before discovery of the sternal wound complication. Organisms cultured from distant sites corresponded to sternal wound cultures in all cases.

The spectrum of cultured organisms showed no particular distribution among the conduit groups or between primary and reoperation patients. *Pseudomonas* infection occurred in 6 of 72 patients (8%): 3 patients with polymicrobial infections, 1 patient with compromised host defenses, and 1 patient with *Pseudomonas* mediastinitis after his first coronary bypass operation. *Serratia* infections occurred in 4 (5.6%) of 72 patients, 3 of whom had *Serratia* as the only organism cultured. Three of these 4 patients had experienced a severe complication before the onset of the wound complication (2 patients had cardiac arrests and 1 patient had long-standing respiratory distress).

In 29 diabetic patients, the distribution of organisms cultured was similar to that of nondiabetic patients, except that seven of eight (88%) polymicrobial infections occurred in diabetic patients. For purposes of uniform data entry, diabetes is defined as clinical diabetes requiring medication. However, the 8 patients with polymicrobial infections fared worse with respect to hospital death (2/8, 25%) (small numbers of patients preclude statistical significance); need for more than one sternal wound revision (6/8, 75%); longest length of hospitalization (median, 83 days) ($p < 0.05$); and concomitant septicemia (5/8, 63%).

Treatment and Outcome

Ten (14%) of the 72 patients who experienced wound complications died in the hospital. Seven of these patients had pneumonia; all had renal failure, and all died from multisystem failure. Cardiac arrest or shock had occurred before the onset of wound complication in 5 of the 10 patients who died. Of 62 survivors, 3 had renal failure requiring dialysis, and 2 of them died in the first postoperative year. Preoperative comorbidity in the form of peripheral vascular disease or diabetes was prevalent in the hospital mortality group, but their preoperative risk was not judged greater than that of the wound complication group as a whole.

Each of the 72 patients was assigned to one of three primary treatment methods: debridement followed by early closure, 41 (57%); muscle or omental flap reconstruction or both, 19 (26%); or debridement followed by open chest and late sternal closure, 12 (17%). Seven (17%) of those treated by debridement and primary closure required reexploration for sternal instability or persistent sepsis, and they underwent flap reconstruction to obliterate dead space after partial or complete sternectomy. Six patients experienced persistent or recurring mediastinal infection up to 6 months postoperatively after discharge. One was treated by drainage alone, but the others required muscle-flap reconstruction. Of the 19 patients who had flap reconstruction initially, 3 (16%) experienced either reinfection or flap necrosis that required revision. There was no significant difference in morbidity among the methods of surgical treatment, but mortality was zero after open treatment compared with 7/41 (17%) for closed treatment and 3/19 (16%) for flap reconstruction. The median length of hospital stay was insignificantly shorter for the closed method (42 days) versus the open method (57 days) or the flap method (46 days).

Economic Implications

We compared hospital charges for all patients with no complications with that for the 72 patients with wound complications. For the latter, the median charge was $58,092 (range, $16,966 to $408,632), which was 2.8 times that of patients with uncomplicated cases. Figure 2 shows hospital charges for patients with sternal wound complications compared with patients with no complications, according to conduit group (ie, vein grafts, a single internal thoracic artery, or bilateral internal thoracic arteries). The hospital charges incurred were not significantly different among conduit groups or between primary and reoperation patients with wound complications. In 1987 dollars, charges substantially exceeded reimbursement. The 43-day median length of hospital stay, five-day median length of intensive care unit stay (range, one to 152 days), and charges for multiple operations explain the increased hospital charges, which do not include physician fees.

We analyzed why 11 patients received vein grafts only. Four of the 11 patients were undergoing reoperation and had left internal thoracic artery bypass grafts performed previously. The other patients were considered higher risk and consequently had vein grafts only because of old age, diffuse arterial disease, poor left ventricular function, chronic renal failure, or chronic obstructive pulmonary

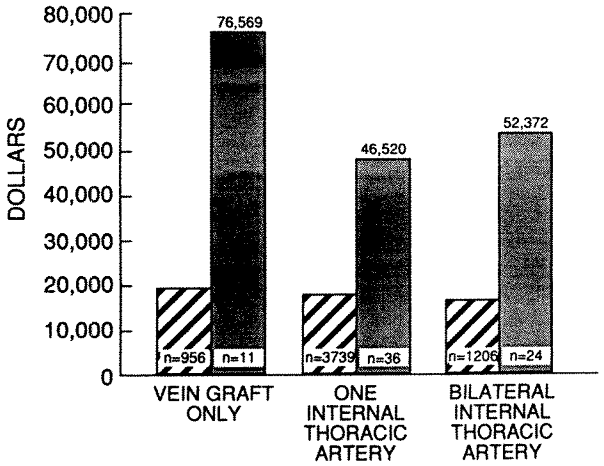

Fig 2. Hospital charges incurred for all wound-complication patients by conduit group compared with uncomplicated patients in those groups. Charges for complicated cases markedly exceeded reimbursement and, overall, amounted to 2.8 times charges for uncomplicated cases.

Table 3. Variables In Wound Complication Patients Grouped According to Bypass Conduit Received[a]

Variable	Vein Graft (n = 11)	1 ITA (n = 38)	2 ITAs (n = 23)	p Value
Age (yr)	68.5	62.9	55.3	<0.002
Diabetes	2 (18)	16 (42)	11 (48)	NS
Peripheral vascular disease	3 (27)	9 (24)	4 (17)	NS
Septicemia	10 (91)	10 (26)	6 (26)	<0.001
Mortality	4 (36)	3 (8)	3 (13)	<0.001
Median length of hospital stay (days)	51	43	38	NS
Cost ($)	84,811	62,683	50,465	NS

[a] Numbers in parentheses are percentages.

ITA = internal thoracic artery; NS = not significant.

disease. The vein graft cohort fared worse in terms of hospital mortality and further morbidity (after diagnosis of wound complication; Table 3). More of these vein graft patients had septicemia, and for this subset of 11 patients, costs were higher than those incurred by either of the two internal thoracic artery cohorts.

Late Follow-Up

Follow-up information was obtained for all patients with wound complication. For the 62 survivors, the mean follow-up was 25.5 months. Figure 3 shows 3-year actuarial survival, including causes of death. In addition to the initial 14% hospital mortality, there was substantial mortality within the first postoperative year. Late sepsis accounted for one of these deaths. Of the 3 initial hospitalization survivors who had been undergoing renal dialysis preoperatively, 2 had a history of chronic renal failure preoperatively; both died in the first postoperative year. Thus, need for renal dialysis among patients with sternal wound complications carried a grave prognosis. Survival based on organism cultured showed that patients with negative cultures had a 91% 3-year survival compared with 62.5% to 69.0% survival for the patients with positive cultures. Overall, the 3-year survival was 75%, which is significantly below previously reported 5-year and even 10-year survival for isolated coronary bypass patients.

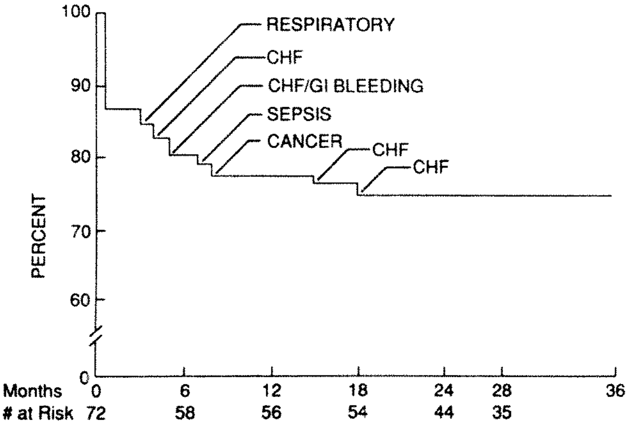

Fig 3. Three-year actuarial survival including all causes of death for entire series. In addition to the 14% hospital mortality, mortality in the first year was substantial and suggests an effect of hospital morbidity. (CHF = congestive heart failure; GI = gastrointestinal.)

Risk Factors for Sternal Wound Complications

In 6,504 consecutive isolated coronary bypass patients operated on from 1985 through 1987, we chose 29 definable clinical, angiographic, and operative variables and subjected them to univariate analysis (Appendix 1). We compared the 72 patients who experienced wound complications with their counterparts who experienced no wound complications. The univariate comparisons were calculated for the entire series, for 5,369 primary patients, and for 1,135 patients who had reoperations. Variables of preoperative steroid medication (2 patients) and tracheostomy (1 patient) were not included, nor was preoperative hospitalization (median, two days in both groups). Twelve variables that achieved significance of $p \leq 0.20$ were subjected to logistic regression analysis. Multivariate analysis identified four clinical factors that significantly increased the probability of wound complication after isolated coronary bypass grafting.

Bilateral internal thoracic artery grafting increased the risk of wound complication only in the presence of diabetes (relative risk, 5.00; 95% confidence interval [CI], 2.4 to 10.5). Bilateral internal thoracic artery grafting in nondiabetic patients carried no greater risk than that found with vein grafts only or with one internal thoracic artery graft. Conversely, diabetes was not implicated in wound complications in patients with vein grafts only or with one internal thoracic artery graft.

Obesity, defined as a body weight ≥20% above normal body weight adjusted for height and frame, carried a relative risk of 2.90 (95% CI, 1.8 to 4.8). Operating time, defined as the time under anesthesia, raised the relative risk of sternal wound complication 1.47 times (95% CI, 1.3 to 1.7) per hour of operating time. Blood transfusion was determined as units of blood or blood products received before the diagnosis of wound complication. Each unit transfused raised the probability of sustaining a wound complication 1.05 times (95% CI, 1.01 to 1.10). For example, 5 U of blood transfused during the perioperative period would increase the relative risk 1.26 times that of a patient who received no blood.

The above determinants applied to all 72 patients with sternal wound complications. Bilateral internal thoracic artery grafting in diabetic patients, obesity, blood units transfused before wound complication diagnosed, and prolonged operation time increased risk of wound complications significantly among primary cases. In the reoperation group, prolonged operation time and obesity were the only factors that significantly elevated the risk of wound complication.

Comment

Approximately 80% of nosocomial infections fall into these four categories: urinary tract infection, surgical wound infection, pneumonia, or bacteremia [2]. Almost three quarters of nosocomial infections occur among surgical patients [3]. A 10-year prospective study [4] concluded that the following preventive maneuvers, listed chronologically, reduce surgical wound infection rates: (1) short preoperative hospitalization; (2) showering with antiseptic soap before operation; (3) shaving of patient kept to a minimum; (4) contamination eschewed; (5) punctilious surgical techniques; (6) as expeditious an operation as is safe; (7) scrupulous care in operations performed on elderly, obese, malnourished, and diabetic patients; (8) no drains brought out through the operative wound; (9) meticulous electrosurgical coagulation technique; and (10) informing each surgeon of his or her clean wound infection rates and average rates among peers.

Mediastinitis After Coronary Bypass Grafting

The severity of illness in surgical candidates may be worsening, but preoperative length of stay and cachexia seen frequently in the early years of cardiac surgery, prophylactic tracheostomies, frequent use of steroids, prolonged operating time for simple cardiac operations, trauma from earlier extracorporeal circulation, prolonged mechanical ventilation, high rates of dehiscence, massive blood transfusions, and the "pump lung"—all of which probably increased the incidence of wound complications—have diminished greatly in practice today.

Numerous reports have exposed the risks, lethal potential, and treatment difficulties of mediastinitis after coronary artery bypass grafting. Aside from the choice of bypass conduit type used in coronary artery bypass grafting, certain clinical variables have been identified (some more consistent than others) as probable causative factors in sternal wound complications. As the method of investigation and weight of statistical power vary from one report to another, we have summarized causative variables in no particular order.

Duration of the operative procedure is implicated in some studies [5, 6] but not all [7, 8]. It is logical, however, that the risk of contamination would be greater in prolonged operation. Inoculation is presumed to occur intraoperatively, but the source is rarely found. From our investigations, we find that catastrophic events followed by low cardiac output or multisystem failure may signal increased risk of sternal wound complication.

Diabetes appears in our experience as an independent risk factor for sternal wound complications, and the risk is significantly greater among patients who received bilateral internal thoracic artery grafts. Diabetic patients who require use of an intraaortic balloon pump are more prone to wound complications. Despite these findings, the early results of operations are only slightly less favorable for diabetic patients [9].

A prospective study of factors predisposing to sternotomy complications [7] did not identify either diabetes or internal thoracic artery grafting (mainly one internal thoracic artery graft) but found that obesity was a major risk factor for sternal and leg wound complications. Our results confirm obesity as an independent risk factor for both primary and reoperation cases.

Exploration for hemorrhage figures prominently among risk factors reported in mediastinal infections [5, 6, 10]; however, this finding is based on series from one institution. Reexploration for bleeding was not statistically significant in either univariate or multivariate analysis in our series from 1985 through 1987.

Reoperation, in contrast to primary coronary artery bypass grafting, has similarly been linked to sternal wound complications. Many investigators referred to in a review by Sarr and co-workers [11] found higher rates of mediastinitis; whereas Wilson and associates [7], Grossi and co-workers [10], and ourselves did not find significantly more wound complications in patients undergoing reoperation.

Prolonged low cardiac output is reported frequently [6, 10, 11] as a causative factor in wound complications and as a herald of other complications. Although we could not identify low cardiac output per se as a causative factor, 5 of the 10 patients who died in the hospital during initial treatment experienced cardiac arrest or shock before the onset of wound complication.

Respiratory complications manifested as ventilation prolonged beyond 24 to 48 hours carry a higher probability of wound infection [10]. Nasopharyngeal cultures [5] have been correlated with organisms from the infected mediastinum and may explain why patients with chronic obstructive pulmonary disease are at higher risk. Prolonged respiratory support indicates a longer stay in the intensive care unit and is associated with a greater likelihood of contamination. In our experience, respiratory complications did not cause a higher incidence of wound problems, but respiratory distress and pneumonia occurred frequently after discovery of a wound complication. We postulate that the best defenses against respiratory complications are: (1) good myocardial protection, which lessens the incidence of low cardiac output, intraaortic balloon pump usage, and prolonged ventilation; (2) blood conservation and judicious use of crystalloids; and (3) secure sternal closure with 19-gauge stainless steel wire (0.80 to 0.89 mm).

Advanced age has been reported as a risk factor infrequently but was not a factor in our series or in most others.

Internal thoracic artery mobilization from the chest wall was implicated early on by Culliford and others [6], who found a 1.1% incidence of mediastinitis in patients who had saphenous vein grafts, a 2.3% incidence in single internal thoracic artery implantation, and an 8.5% incidence after bilateral internal thoracic artery implantation. Sternal ischemia and a higher rate of bleeding requiring return to the operating room were cited by Culliford and associates as predisposing factors.

Arnold's study of the sternal blood supply [12] suggested that bilateral internal thoracic artery mobilization may render the sternum avascular. Subsequently, Grmoljez and Barner [13] refuted Arnold's conclusion on the grounds that he ignored the intercostal collateral flow through the periosteal plexus. In their experience, patients who underwent single internal thoracic artery grafting or bilateral internal thoracic artery grafting showed only a 4% rate of wound complication. Recently, the subject was raised again by Seyfer and collaborators [14], who measured sternal blood flow in rhesus primates using 15-μm microspheres. Blood flow was unchanged after median sternotomy, but mobilization of one internal thoracic artery caused a 90% decrease in blood flow within that sternal half, and no electrocautery was used. Furthermore, these investigators could not find collateral flow that could substitute for the loss of internal thoracic artery blood supply.

Sometimes theory conflicts with practice. The statement, "complete bilateral mobilization to the level of the subclavian arteries is certain to render the bone avascular" [12], if correct, explains the cause of infection in a minuscule number of patients. Through a 20-year experience, we have not observed that internal thoracic grafting per se causes sternal would complications. However, we found a higher rate of wound complications with bilateral internal thoracic artery grafting in diabetic patients. In this series, nondiabetic patients who underwent bilateral internal thoracic artery grafting had no greater risk of wound complication than patients with one internal thoracic artery or vein grafts only.

A recent clinical finding from New York University [10] showed that inclusion of an internal thoracic artery did not increase the risk of wound complication. Green and co-workers [15] have reported that the incidence of wound complication is not affected by single or bilateral internal thoracic artery use.

Perioperative Measures

As experience is acquired in arterial bypass grafting, thoracic arterial conduits become less implicated as a causative factor in wound complication. In cardiothoracic surgery, any discussion of wound problems invariably returns to perioperative technique. These perioperative measures have been documented to reduce rates of sternal wound complications: (1) showering preoperatively with use of a skin disinfectant; (2) replacement of shaving with an electric clipper or chemical depilation; (3) confinement of hair removal to incision sites only; (4) a short rather than long course of antibiotics [16]; (5) recognition that broad vascular pedicles coupled with costochondral scoring by electrocautery is unnecessary and potentially damaging; (6) attention to intraoperative aseptic protocol, secure sternal closure, and layered approximation of fascia and subcutaneous tissue; (7) use of nonabsorbable vertical mattress skin sutures in diabetic, aged, and disabled patients rather than continuous subcuticular closure (our experience); and (8) targeted wound surveillance by a nurse epidemiologist who reports wound and other nosocomial infections to the individual staff members for group discussion.

For the past 5 years, we have followed the protocol of having surgeons rescrub before closing. This practice arose from the epidemiological studies of Cruse and Foord [4], who found that 12% of surgeons' gloves were punctured at the conclusion of the operation. Whether this tactic has had a major impact is unknown; but with the changing patient profile and the tendency toward longer operations, it is logical to suggest that rescrubbing before closure is a reasonable precaution.

Many other elements of cardiac surgical care do not lend themselves to objective analysis but are clearly important to outcome and risk of infection. Organization and technique affect initial outcome including wound complication rates. These variables include the efficacy of myocardial protection, blood conservation, anesthesia and perfusion technology, number and skill of operating room personnel, traffic flow in operating room suites, intensive care unit structure, sterility, communication, and above all, surgical theater-related technique.

Pathogens in Sternal Wound Complication

There is no justification for prolonging administration of perioperative antibiotics beyond two days. Goldmann and associates [16] found that an additional four days of antibiotics may decrease the incidence of urinary tract infection, but it may be offset by an increased risk of pneumonia. Comparisons of efficacy of antibiotics in preventing postoperative infection have not been particularly illuminating [8].

Gram-positive cocci were the most common pathogens in our series and in the literature on sternal wound complication [11]. Many staphylococcal isolates are susceptible to the antimicrobial drugs used in prophylaxis [17], but the inoculum and virulence probably explain the failure of prophylaxis. The role of the asymptomatic carrier pertains more to epidemics, but 15% of the healthy population are chronic asymptomatic nasal carriers of *Staphylococcus aureus* [18].

In 40% of patients reported on, both gram-positive and gram-negative bacilli were isolated [11]. In our series, only 8 (11%) of 72 patients had polymicrobial cultures, but 7 were diabetic patients. As judged by mortality, septicemia, length of stay, and number of reconstructive operations, this bacterial group had the worst prognosis. We did not determine any significant difference in incubation period or method of presentation between the various bacterial groups, but for 11 (15%) patients in whom no organism was cultured, the wound complications showed significantly earlier than in patients with positive cultures. Also, these patients with negative cultures enjoyed a significantly higher survival than those with positive cultures.

Surgical Treatment and Outcome

The goal of treatment is to debride all infected and avascular tissue and to obliterate dead space. If the mediastinitis or dehiscence is diagnosed early and the sternum is intact, curettage of the sternal edges and drainage of mediastinal infection combined with secure sternal reclosure and irrigation of the retrosternal space may suffice. The closed method predominates today and was used in two thirds of our patients. Of these, 7 (17%) had recurrence of infection necessitating reexploration, drainage, and eventual flap reconstruction up to 6 months after initial hospital discharge.

In the closed method treatment, irrigation is usually continued for three to five days or until the effluent becomes sterile. Irrigants include antibiotic solutions, dilute povidone-iodine, or saline. Of these solutions, dilute povidone-iodine is probably used most frequently because of its effectiveness and because of reports that continuous mediastinal lavage with antibiotics may predispose the patient to fungus infection and antibiotic toxicity. Caution in povidone-iodine treatment is necessary because constrictive pericarditis has been reported.

The open method of sternal wound treatment involves debridement, open packing until a "clean" wound develops, and then exercising options of secondary closure or use of flaps to fill the space with or without a skin graft. Hospitalization is generally prolonged; respiratory complications are prevalent, but overall results are approximately equal to the closed method. Ten of our 12 patients treated by the open method eventually underwent flap reconstruction, 2 of whom required revision owing to reinfection at 3 and 6 months postoperatively. Only 2 healed completely by second intention. Mediastinal infection carries the potential for bypass graft erosion and hemorrhage, especially near the aortic anastomosis. Nonetheless, mediastinitis does not appear to affect overall vein-graft patency.

After radical debridement or sternectomy, the first line of defense for coverage of the upper two thirds of the mediastinum is selection of one or both pectoralis major muscles based on their thoracoacromial blood supply. Transposition of the rectus muscle based on superior epigastric vessels requires an ipsilateral internal thoracic artery. It does not result in severe abdominal wall weakness and is ideal to cover defects in the lower third of the mediastinum. In patients who have not had an internal thoracic artery graft, the rectus muscle may even be transposed to cover the entire mediastinum, either as a muscle alone or as a myocutaneous flap [19]. Muscle flaps may be applied immediately or after an open period of saline dressings. In Pairolero's experience [20], it is the wound condition, not the time of discovery, that dictates whether muscle transposition should be used. Dehiscence without gross suppuration may be treated with mediastinal drainage alone. When debridement of suppurative peel is required, flap transposition is the procedure of choice to obliterate dead space.

Advantages of use of the greater omentum, with its excellent gastroduodental blood supply, apparent angiogenesis factor [21], and bulk, are offset somewhat by the need for a laparotomy, potential for epigastric hernia, and less stabilizing effect compared with muscle flaps. Nevertheless, omental transposition covers large defects and serves as a versatile utility flap or back-up for muscle-flap failure and closure for lower sternal defects when rectus muscle cannot be used.

When bilateral internal thoracic artery grafts have been performed and rectus muscle flaps cannot be employed, detached pectoralis muscle may be used to cover defects in the upper two thirds of the mediastinum, and the omentum may be used for the lower third. In complete sternectomy, it is important to remove the avascular costal cartilages, a major source of persistent infection. In our experience, delayed closure resulted in no hospital mortality, but morbidity was approximately the same and eventual outcome did not differ appreciably between our treatment groups. The seriousness of wound complications extends beyond the initial hospital period. Six discharged patients experienced recurring mediastinal infection up to 6 months postoperatively.

Our hospital mortality of 14% parallels other reports of documented mediastinitis. Multisystem failure preceded by or involving renal failure was the mode of death in all cases. Sternal wound infection increases length of hospitalization more consistently than any other major complication [22] and influences readmission. Hospital reimbursement did not meet charges or costs, and loss of net hospital income may be expected for patients with this complication. Six of the 62 patients discharged alive were readmitted with recurring infection; no particular organism predominated, and most patients required flap construction. The mortality after initial discharge and up to the first postoperative year was nearly as high as hospital mortality. This recent experience underscores the devastation of sternal wound complication, which affects early and late mortality, morbidity, and cost of care.

Infection Surveillance and Control

Targeted infection surveillance and control may reduce nosocomial infection rates by up to one third [23]. As severity of illness in the general patient population worsens, it is incumbent on every surgical group to have a system for reporting surgical wound infection rates back to each department and practicing surgeon. To accomplish this goal, a physician with a special interest in infection control works with nurse epidemiologists to devise an accurate reporting format. Our experience with this program during the past 10 years has been one of continued awareness about all perioperative infections, organisms cultured, and individual surgeons' rates of infection. We have observed consistently that this awareness affects surgeon behavior. As we review infections over the years, including findings in this report, we conclude that a constant appraisal of preventive measures, dissemination of results, and insistence on accountability are the best methods of attaining the "irreducible minimum" [24], given the current state of technology and our understanding of immune function.

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A more complete bibliography is available from Dr Loop.

Appendix 1. Twenty-nine Clinical, Angiographic, and Operative Variables Analyzed in Univariate and Multivariate Analyses

1. Patient age
2. Patient age <70 vs >70 years
3. Height
4. Weight
5. Obesity
6. Sex
7. Diabetes
8. Smoking
9. Hypertension
10. Peripheral vascular atherosclerosis
11. Primary operation vs reoperation
12. Extent of disease (1, 2, 3, left main)
13. Extent of disease (1–2 vs 3 or left main)
14. Left main trunk >50% narrowing
15. Left ventricular function (normal, mild, moderate, severe)
16. Left ventricular function (normal/mild vs moderate/severe)
17. Number of bypass grafts
18. Number of internal thoracic artery grafts (0, 1, 2)
19. Number of internal thoracic artery grafts (0–1 vs 2)
20. Number of units of blood or blood products (all)
21. Number of units of blood (0 vs >0)
22. Number of units of blood (0–1 vs ≥2)
23. Number of units of blood (<4 vs ≥4)
24. Reopen for bleeding
25. Postoperative stroke
26. Postoperative respiratory failure
27. Postoperative renal failure
28. Anesthesia time
29. Intraaortic balloon pump

DISCUSSION

DR HENDRICK B. BARNER (St. Louis, MO): The Program Committee's vision is apparent in their choice for the Maxwell Chamberlain Award. The presentation we have heard and the submitted manuscript fulfill the expectations associated with this honor. Dr Loop and his colleagues at the Cleveland Clinic have once again presented us with a detailed analysis of their superb surgical experience in coronary reconstruction.

What is most impressive is not the low incidence of mediastinal wound complications, but the remarkably low hospital mortality. In a comprehensive review Newman and colleagues at Emory University found that the average hospital mortality in a collected series was double that reported today, with a range of 14% to 52%. For this achievement, Loop and colleagues deserve our praise.

There is yet another salient feature of this presentation. Survival of 86% at hospital discharge fell to 77% in 1 year and 75% in 3 years. This is substantially lower than the reported survival for isolated coronary bypass grafting. This observation suggests an aftermath of mediastinitis not previously recognized and raises the point that hospital mortality may represent an optimistic assessment of outcome in patients suffering this morbid complication. Realistic risk assessment must consider the 1-year outcome in this unfortunate group of patients, and has implications for cost-effectiveness and reimbursement strategies.

Reading the manuscript has prompted examination of our own practices with respect to wound complications and has rekindled our desire to improve them. Dr Loop, would you relate your antibiotic regimen during this study? Is timing of the first dose important; that is, should it be given in the nursing unit or operating room? Are antibiotics added to the pump prime? Are they repeated intraoperatively at a set interval during longer operations? If these practices differed among surgeons, was outcome affected? Perhaps these are not important issues.

Additionally, do you use bone wax? Do you have special suture techniques for reclosure of the infected sternum after debridement? Do you have a standardized protocol for catheter irrigation of the mediastinum in the closed management method that you used successfully in two thirds of your patients with only a 17% recurrence rate?

Can you define criteria used for selection of one of the three principal methods of wound management when infection does occur, or is this best defined as clinical judgment?

And finally, with regard to bilateral internal thoracic artery grafting, what are your recommendations to us and to your patients? Do we avoid bilateral internal thoracic artery grafts in all diabetic patients or in only those who are also obese? Should younger diabetics be offered bilateral internal thoracic artery grafts? In short, should this information be used to guide conduit selection or rather to inform certain patients of added risk?

DR GEORGE E. GREEN (New York, NY): The work presented by Dr Loop is a model of scholarly and clinical achievement. I would like to endorse his conviction that bilateral internal thoracic artery grafts can be done with no increase in thoracic morbidity. We have not employed the admirable cardiovascular information retrieval method that Dr Loop has at the Cleveland Clinic, but have reviewed two consecutive series of 100 patients: one beginning in August 1985, when we thought it was appropriate to attempt routine bilateral mammary grafting, and one beginning in January 1988.

In the first group, when we began this study, 80 of the 100 patients did have bilateral internal thoracic artery grafts. In that group, no patient became infected.

In the second group, beginning in January 1988, there happened to be an unusually high incidence of insulin-dependent diabetics (18 of the 100 patients). In that group, 88 patients had both internal thoracic arteries used as grafts. There was one infection. That was not in a diabetic patient, but in a patient in whom an extreme hypoxic reaction to the use of the pump oxygenator developed and who required assisted ventilation for 1 week. Bilateral pneumothoraces developed, and the patient became infected and required omental grafting for reconstruction. He is well 18 months later.

I congratulate Dr Loop on his work and I certainly endorse his conviction that both internal thoracic arteries can be used in most patients most of the time without an increase in morbidity.

DR EUGENE A. GROSSI (New York, NY): At our institution, we have also studied a similar cohort of patients but have different results. At our institution, 2,300 patients underwent isolated revascularization. Vein grafts alone were reserved for more elderly patients and those with hemodynamic instability. The mean age of this group was approximately 10 years greater.

Our overall infection rate was 1.6%, similar to that reported by Dr Loop and associates. However, for patients who had at least one mammary artery graft, there was a 2.2% risk of infection, and for those with no mammary artery graft, the risk of infection was 0.8%. We also noted that the course of infection was more severe in those patients who had a mammary graft, with the hospitalization being significantly longer.

Logistic regression revealed that the use of double internal mammary artery graft was the strongest risk factor for infection, with a relative risk of 4.4%, followed by the presence of diabetes and the use of a single graft. In contrast to the data of Loop and associates, our data suggest that the use of an internal mammary artery graft does increase the risk of serious infection.

Our question to Dr Loop is have you found it necessary to be more aggressive in debridement or alter your initial approach to sternal infections in patients with internal mammary artery grafts?

DR PETER C. PAIROLERO (Rochester, MN): I, too, would like to congratulate Dr Loop and his associates for a very timely presentation on wound complications after coronary artery bypass grafting. Clearly, they have delineated the incidence of infection with respect to type of conduit and have further elucidated the relative risk factors that lead to this complication.

They fall short, however, in describing how best to treat this infection. Wound complications represent a spectrum ranging from early cellulitis, to intermediate mediastinitis, to finally late osteochondritis and costochondritis. Each stage can and should be managed differently. To lump all infections together and then try to decide which method of management is best tends more to confuse rather than to elucidate the treatment. Loop and associates are, I know, aware of the spectrum but failed to elaborate on it.

Early infection manifested by cellulitis often without cultureable pathogens can usually be treated by debridement and primary closure. Eighty-three percent of the patients in this study who were treated this way were treated successfully. Dr Loop, were these 83% early infections? Also, what was the initial stage of the wound in the 17% who failed to respond? One fifth of your infections occurred in patients who had left the hospital. How were these patients treated? Were they the ones who did not respond?

Finally, in contrast to cellulitis, mediastinitis and osteomyelitis should be treated by thorough debridement and then muscle transposition to obliterate mediastinal dead space. This was the initial management in over 25% of the patients of Loop and associates, but still 16% of the treatments failed. Why? Were these patients adequately debrided? In our experience, failure to remove all foreign bodies and necrotic and infected bone is the single largest reason for late recurrence of infection.

DR LOOP: Dr Barner has underscored the aftermath of mediastinitis that we emphasized in our paper. We used cefamandole during the 3 years of survey. It was administered at the outset of the operation, and if the operation was prolonged, this antibiotic was given again before closure.

Bone wax is used routinely. We advocate no particular technique of wound closure after debridement. Irrigation is with either dilute povidone-iodine (Betadine) or saline solution. I prefer saline solution.

In regard to your question about indications for bilateral internal thoracic artery grafting, we believe that expanded use of the internal thoracic artery should become routine for younger patients. We do inform diabetic patients who require a bilateral thoracic artery that their risk of infection is slightly higher.

We have been stimulated by Dr Green's excellent results in the use of both internal thoracic arteries, and I believe that he, as well as anyone, has shown that meticulous technique ensures the irreducible minimum in infection rates. Bilateral thoracic artery grafts are used preferentially in his practice and in ours. Dr Grossi and his colleagues at New York University have contributed enormously to our knowledge about mediastinal wound complications.

We could not show any difference in the three methods of surgical treatment for mediastinitis and we found no difference in the late results after these treatments. Dr Pairolero mentioned that we found that no particular treatment was best. As we have learned from him, the treatment used depends on the condition of the wound at the time of the discovery. Each of these methods of treatment are applicable in individual cases. The people with recurring sepsis probably did not have adequate debridement at the time of their initial closure, and most of these people had either recurring sepsis from costochondritis or flap necrosis. All of them were eventually treated by flap reconstruction.

I wish to close by mentioning two technical points. There is a large epidemiologic study reporting that 12% of the surgeons' gloves were punctured by the end of the operation. This finding has led most of our group to follow a protocol of having surgeons rescrub before they close the sternum and the superficial tissues.

The last point is that we use interrupted polypropylene skin sutures for patients who are elderly, debilitated, or obese, patients receiving bilateral internal thoracic artery grafts, and especially diabetics. These sutures may be left in for 14 to 21 days, depending on the patient and the condition of the wound, and this method has virtually eliminated superficial infections.

Routine Use of the Left Internal Mammary Artery Graft in the Elderly

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Left internal mammary artery (LIMA) grafts have better long-term patency rates than do saphenous vein grafts and result in improved late survival. The present study was undertaken to assess the results of LIMA grafting in the elderly. From 1980 through 1988, 723 patients 70 years of age or older had isolated coronary artery bypass grafting performed. During the first 5 years, only 11% of the elderly patients received LIMA grafts, whereas 86% having coronary artery bypass grafting since 1985 had LIMA grafts. Since 1986, LIMA use in the elderly has become routine, with 92% of patients receiving internal mammary artery grafts. During the first 5 years, elderly patients had a hospital mortality rate of 9.3%. Since 1985, the hospital mortality rate fell to 5.5%. In addition, the occurrence of major surgical complications was either unchanged or reduced in patients receiving LIMA grafts. Furthermore, late follow-up indicates a significantly improved 4-year survival rate in patients with internal mammary artery grafts compared with those without: 86 ± 0.02% versus 77 ± 0.03% ($p < 0.01$). Analysis of multiple potential risk factors for early mortality was performed using multiple logistic regression and late survival using the Cox proportional hazards model. Although unmeasured predictor variables may confound retrospective analyses, LIMA grafting appears to be an independent predictor both of improved early and late survival.

(Ann Thorac Surg 1990;49:188–94)

In patients requiring coronary artery bypass grafting, the internal mammary artery (IMA) is widely accepted as the best conduit for use as a bypass graft [1–3]. General acceptance of the IMA as the bypass graft of choice is based on relatively recent demonstrations of improved late patency compared with vein grafts [4–8] as well as improved late survival among grafted patients [9, 10]. Because the focus of the apparent benefit of the IMA graft compared with vein grafts has been on improved patency and survival late after the initial bypass operation, many surgeons have avoided the use of the IMA graft in elderly patients, assuming that it would provide no substantial benefit for patients with a limited long-term outlook [11, 12]. Additionally, there has been the perception that IMA grafting in elderly patients may be associated with greater risks of noncardiac complications and thus may be inappropriate [13].

The number of elderly patients being referred and accepted for operation has risen dramatically in most centers over the past decade. Patients 70 years old and older often constitute more than 20% of the total group of patients having coronary bypass grafting, and these elderly patients often have increased risk of surgical complications or death [14, 15]. On the other hand, the number of elderly patients surviving for up to 5 years after operation is comparable with 5-year actuarial survival estimates for patients in their fifth and sixth decades of life [16]. Furthermore, elderly patients who undergo successful coronary bypass grafting appear to have a relative probability of survival that is greater than their age-, race-, and sex-matched counterparts in the general population [16]. Therefore, failure to use an IMA graft in an elderly patient based on a presumed lack of importance of late patency characteristics of the IMA versus the vein graft may be incorrect. Since 1985, use of the left internal mammary artery (LIMA) graft in patients undergoing coronary bypass grafting in this hospital has become routine, regardless of the age of the patient. The present review and analyses were undertaken to assess the results of routine LIMA grafting in the elderly to determine whether such a policy has resulted in any change in early survival, surgical complications, or late survival in patients 70 years old and older.

Material and Methods

From January 1980 through December 1988, 723 consecutive patients aged 70 years or older underwent isolated coronary artery bypass grafting at the Johns Hopkins Hospital. All of these patients were entered into the present case control study and a longitudinal follow-up was undertaken to assess the results of IMA grafting compared with the results of bypass grafting in patients in whom only vein grafts were implanted. Patients studied include those undergoing routine, urgent, or emergent bypass grafting. Any patient undergoing coronary artery bypass grafting in combination with another surgical procedure, such as valve replacement, aneurysm resec-

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tion, or carotid artery operation, was by definition excluded from this study.

All operations were performed through a median sternotomy incision and used standard extracorporeal perfusion techniques. Bubble oxygenators were used for most patients and moderate systemic hypothermia (25° to 30°C) was employed in all cases. Cold crystalloid potassium cardioplegia along with intermittent or continuous topical myocardial cooling with cold saline solution were employed for myocardial protection. Venting of the main pulmonary artery with a small sump-type suction catheter was used in the majority of patients.

Detailed preoperative, intraoperative, and postoperative data were collected on all patients by an experienced clinical analyst using the data collection system in place in the Division of Cardiac Surgery. Details of the patient's medical history including history of previous myocardial infarction, the presence of coronary risk factors, and associated medical conditions were noted. Also recorded were the nature of the patient's preoperative anginal syndrome, either absent, stable, or unstable, whether the patient required coronary care unit admission before coronary bypass grafting, and whether the patient had an intraaortic balloon pump placed before operation. The nature and extent of the coronary arterial involvement was recorded as was preoperative left ventricular function, determined either by left ventriculography or multigated acquisition scanning. Intraoperative information recorded on all patients included the number of grafts performed, whether the LIMA was used, the duration of cross-clamping, the duration of cardiopulmonary bypass, and the incidence of perioperative hypotension. Postoperative information recorded on all patients included the incidence of reoperation for bleeding, the incidence of sternal wound infection (defined as median sternotomy incision infection down to or involving the sternum), the need for inotropic drug support, the need for prolonged ventilation, the need for dialysis, the incidence of arrhythmias, the length of postoperative stay, and the operative mortality rate (defined as death within the first 30 days after operation or death occurring any time during a continuous hospitalization after operation).

Follow-up data were obtained by telephone interview using a standardized format, which was read verbatim to the patients or respondents. Follow-up information was gathered successfully on 99.1% of patients in the late survival study.

Preoperative and intraoperative variables and postoperative outcomes were examined and compared between the two study groups, those patients having the LIMA bypass graft as part of their coronary bypass procedure and those without an IMA graft. All variables were considered univariately using either a χ^2 test for categorical variables or Student's *t* test for continuous variables to determine their effect on surgical mortality and other postoperative complications. Those variables found to be significant at a level of $p < 0.1$ and those variables known from other studies to be important potential predictor variables of survival were entered into the multiple variable analysis. The correlations of possible predictor variables were examined subsequently to avoid the problem of multicolinearity. Multiple possible predictor variables of operative mortality, that is, either 30-day or in-hospital mortality, were analyzed using multiple logistic regression analysis. Variables were added stepwise with a *p* value for entering of 0.10 and a *p* value for removing of 0.15.

Survival status at the time of follow-up was compared between the two groups using Kaplan-Meier survival curves. Possible variables affecting late survival were also examined univariately for their influence on long-term survival using the log rank method of comparing groups. As with the analysis of predictors of surgical mortality, variables found to be significant at a level of 0.1 were entered into the multivariate analysis. Multiple possible predictor variables of long-term survival were considered using the Cox proportional hazards model.

Table 1. Preoperative Data

Variable	Vein Grafts Only (n)[a]	Internal Mammary Artery Grafts (n)[a]	*p* Value
Total patients	270 (37.3)	453 (62.7)	
Mean age (yr)	73.6	73.7	0.556
Female	93 (34.4)	150 (33.1)	0.775
Prior myocardial infarction	170 (63.2)	306 (67.9)	0.232
Prior coronary artery bypass grafting	4 (1.5)	14 (3.1)	0.273
Unstable angina	154 (58.6)	302 (72.1)	0.004[b]
Ejection fraction (%) (mean ± SD)	61.8 ± 16.1	55.0 ± 16.5	0.001[b]
Preop Coronary Care Unit	83 (30.7)	105 (23.2)	0.032[b]
Preop intraaortic balloon pump	32 (11.9)	25 (5.5)	0.004[b]
Diabetes	62 (23.2)	96 (21.2)	0.598
Cerebrovascular disease	75 (28.1)	117 (26.0)	0.600
Peripheral vascular disease	64 (23.9)	98 (22.1)	0.653
Other medical illness	178 (65.9)	353 (77.9)	0.001[b]

[a] Numbers in parentheses are percentages. [b] *p* values ≤0.05 indicate a statistically significant difference between groups.

SD = standard deviation.

Results

Preoperative Data

As noted in Table 1, nearly two thirds of elderly patients undergoing isolated coronary artery bypass grafting between 1980 and 1988 had at least one IMA graft placed. As seen in Figure 1, most of the patients receiving IMA grafts (94%) underwent operation between 1985 and 1988. On the other hand, 75% of patients with vein grafts only underwent operation between 1980 and 1984.

When comparing preoperative characteristics of those patients receiving vein grafts only with those of patients receiving at least one IMA graft (Table 1), no significant differences were noted in the mean age of the patients, sex, or cardiac history with respect to previous myocardial

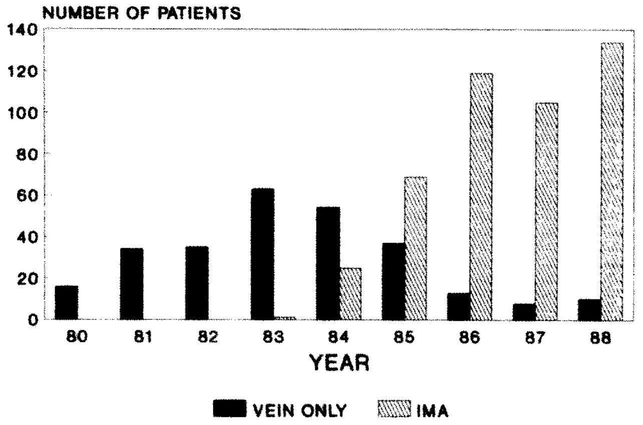

Fig 1. Annual distribution of elderly coronary bypass patients receiving either vein grafts only or an internal mammary artery graft plus vein grafts (IMA) from 1980 to 1988.

infarction. Although the IMA patients were noted to have a significantly higher occurrence of other medical illnesses, neither group had a higher incidence of preexisting diabetes or other conditions associated with atherosclerosis. The number of IMA patients who had unstable angina was significantly greater than that in the vein graft group, and the mean ejection fraction in the IMA patients was significantly less, although the mean ejection fractions for both groups were in a nearly normal range. In spite of a significantly greater number of IMA patients with unstable angina, a higher percentage of vein graft patients had been admitted to the Coronary Care Unit before operation. Furthermore, nearly 12% of the vein graft patients had an intraaortic balloon pump placed before operation compared with 5.5% of the IMA group.

Operative and Postoperative Data

The operative courses of both groups of elderly patients as reflected by bypass pump time were not different, as seen in Table 2. There were, however, several significant differences with respect to postoperative events and complications. Hospital mortality was significantly greater in patients receiving vein grafts only (9.7% versus 4.9%). The incidence of stroke with persistent neurological deficit was also significantly greater in patients receiving vein grafts only. Renal failure requiring dialysis occurred in twice as many patients having vein grafts only, but the difference in occurrence rates between the two groups was not statistically significant. Likewise, the incidence of sternal wound infection, although twice as great in the vein graft only group (3.7%) compared with the IMA group (1.8%), was different only at a p value of 0.15. The occurrence of postoperative myocardial infarctions was not different between the two groups. Significantly more patients in the IMA graft group, however, received inotropic drugs after operation compared with the patients without IMA grafts. Reoperation for bleeding occurred nearly twice as often in vein-graft-only patients (6.3%) compared with only 3.8% in the IMA group ($p = 0.15$). Finally, the mean length of stay for IMA patients was slightly shorter compared with the mean postoperative hospitalization for vein graft patients (12.7 versus 14.2 days, $p = 0.067$).

Table 2. Operative and Postoperative Data

Variable	Vein Grafts Only (n)[a]	Internal Mammary Artery Grafts (n)[a]	p Value
Bypass pump time (mean ± SD)	115.5 ± 29.6	114.9 ± 32.2	0.804
Postop inotropes	38 (14.1)	108 (23.9)	0.003[b]
Reoperation for bleeding	17 (6.3)	17 (3.8)	0.150
Sternal wound infection	10 (3.7)	8 (1.8)	0.165
Stroke	20 (7.5)	12 (2.7)	0.005[b]
Postop dialysis	8 (3.0)	6 (1.3)	0.200
Postop myocardial infarction	11 (4.1)	14 (3.1)	0.618
Length of stay (mean ± SD)	14.2 ± 10.3	12.7 ± 12.1	0.067
Mortality	26 (9.7)	22 (4.9)	0.019[b]

[a] Numbers in parentheses are percentages. [b] p value ≤0.05 indicates a statistically significant difference between groups.

SD = standard deviation.

Table 3. Multiple Logistic Regression Analysis for Hospital Death

Variable	p Value	Estimated Relative Risk
Year of operation	0.53	. . .
Sex	0.58	. . .
Age	0.89	. . .
Ejection fraction	0.39	. . .
Diabetes	0.48	. . .
No IMA graft	0.05	1.44
IABP	0.01	1.84
Unstable angina	0.05	1.72

IABP = intraaortic balloon pump; IMA = internal mammary artery.

Analysis of Operative Risk

The possible predictor variables of surgical mortality, that is, deaths occurring within 30 days of operation or during the same hospitalization after bypass grafting, were analyzed using multiple logistic regression techniques. As noted in Table 3, only three variables were predictive of hospital death after coronary artery bypass grafting. The presence of unstable angina and even more significantly the need for an intraaortic balloon pump preoperatively were associated with an increased risk of hospital death, as was the absence of an IMA graft. None of the other possible predictor variables correlated significantly with increased risk of death, including age or sex of the patient, the year in which the operation was done, the patient's preoperative ejection fraction, or the presence of diabetes mellitus.

Analysis of Late Survival

When possible predictor variables of late survival were subjected to multiple logistic regression analysis, the

Table 4. Multiple Logistic Regression Analysis of Late Survival

Variable	p Value
Year of operation	0.48
Sex	0.95
Diabetes	0.48
Age	0.08
Ejection fraction	0.01
IMA graft	0.02

IMA = internal mammary artery.

improvement in late survival correlated significantly with the presence of an IMA graft in this group of elderly patients (Table 4). The patient's preoperative ejection fraction was also significantly predictive, whereas older age was suggestive of poorer survival, at a p value of 0.08. Neither the sex of the patient, the year in which the operation was done, nor the presence of diabetes was useful in predicting late survival among these elderly patients.

As shown in Figure 2, the Kaplan-Meier survival estimates showed rather striking differences in survival between the group of patients receiving IMA grafts and those receiving vein grafts only at each of the first 4 years of follow-up. Actuarial estimates were not made beyond 4 years for patients receiving IMA grafting due to the small number of IMA grafts used before 1985.

Patients Excluded From Internal Mammary Artery Grafting

From January 1986 through December 1988, 389 elderly patients, or 54% of the entire elderly group analyzed in this review, underwent isolated coronary artery bypass grafting. Of these 389 patients, 92% or 358 patients received LIMA grafts. Two of the 31 patients without LIMA grafts (6.5%) and 16 of the 358 patients with LIMA grafts (4.5%) died after operation. As seen in Table 5, among the 31 patients who did not receive an LIMA graft, 6 patients either had no left anterior descending coronary artery disease or had had a previous LIMA graft placed at the time of an initial coronary artery bypass grafting procedure. Five patients without LIMA grafts went to the operating room hemodynamically unstable and were not believed to be candidates for LIMA harvesting. In 6 additional patients, the operating surgeon chose not to harvest the IMA because of diabetes mellitus and the patients' requirements for insulin or because of chronic steroid therapy. In 3 patients, previous left mastectomy and chest wall irradiation had been performed for breast carcinoma, and in 4 other patients a single surgeon elected not to use an IMA graft. In the remaining 7 patients, either injury to the IMA occurring during harvesting or inadequate length to allow for anastomosis was thought to preclude its use. In no patient was the IMA harvested and not used because of inadequate blood flow.

Table 5. Exclusions From Left Internal Mammary Artery Grafting: 1986–1988[a]

Cause	Number of Patients
No left anterior descending coronary artery	5
Hemodynamic instability	5
Inadequate LIMA length	4
Injury to LIMA	3
Prior use	1
Previous chest wall irradiation	3
Medical conditions (insulin-dependent diabetes, chronic steroid treatment)	6
Surgeon's "preference"	4

[a] During this period, 389 elderly patients underwent coronary artery bypass grafting; 31 did not receive internal mammary artery grafts.

LIMA = left internal mammary artery.

Comment

The decision to adopt a policy of routine IMA grafting in elderly patients, made by this surgical group about 5 years ago, was based on several theoretical and practical considerations. Clinical and angiographic follow-up data that

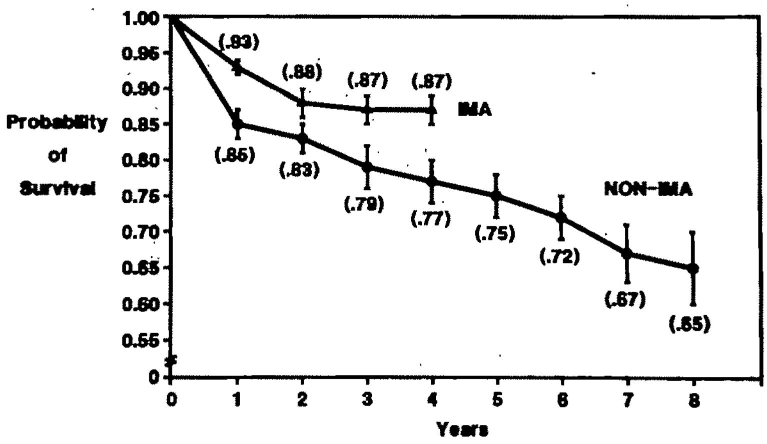

Fig 2. *Actuarial Kaplan-Meier survival estimates for coronary bypass patients 70 years and older with internal mammary grafts (IMA) or vein grafts only (NON-IMA). Projected survival for up to 4 years is significantly better for IMA patients.*

emerged during the early 1980s comparing patency characteristics of IMA versus vein grafts demonstrated, among other things, that both early and late patency of the IMA graft were better than those with vein grafts (4–8). Because early graft patency is improved with IMA grafts, some immediate advantage might accrue to a small subset of patients due to enhanced left anterior descending coronary artery graft flow with IMA versus vein grafts [5]. On a more practical level, it was apparent that in many elderly patients, the greater saphenous vein is a poor-quality bypass conduit. On the other hand, the IMA generally proved to be an excellent conduit, especially in elderly female patients, who often have relatively poor greater saphenous veins.

In addition, data generated in a review of our own experience with coronary artery bypass grafting in the elderly, completed in 1985, pointed out that although patients older than 70 years had a substantially higher operative risk than younger patients, late survival characteristics of the elderly were similar to those of many younger patients, and in fact were better than age-matched patients in the general population based on US Life Table data [16]. The extensive late survival data from the Cleveland Clinic, reported in 1986 by Loop and associates [9], demonstrated significant improvement in 10-year survival for IMA versus non-IMA patients. Actuarial data from the same study suggested that improvement in survival between the two patient groups became apparent as early as 4 or 5 years after coronary artery bypass grafting. These data and our growing satisfaction with the IMA graft as a superior bypass conduit in many elderly patients resulted in the current policy of routine IMA grafting regardless of age.

The early outcome after operation in the elderly patients in this series clearly was better when the LIMA was used for anterior wall revascularization. The reduction in operative mortality from 9.7% to 4.9% in IMA patients was highly significant, with the IMA graft being one of several independent predictors of the improvement in survival. Most of the patients receiving IMA grafts underwent operation subsequent to 1983, theoretically flawing the comparison of outcome with that of those patients with vein grafts only. It is likely that during this 9-year period, there were additional surgical or management factors that contributed to the decline in operative risk. Such additional influences on surgical mortality have not been identified, however, and if present, they are likely to be less important than the adoption of routine IMA use in this patient group. In addition, analysis of these data fail to establish a significant correlation between the year in which the operation was performed and outcome in terms of surgical mortality.

The present analysis of early outcome also supports the safety of routine IMA use in elderly patients. In virtually all outcome and complication categories, routine IMA use was as safe as or safer than vein grafting alone. Refinements in such things as titration of heparin effect, reduced blood and factor administration, and alterations in routine cardiopulmonary bypass perfusion support to use pulsatile flow in the elderly patients at greater risk of stroke may account for some outcome improvements in patients operated on in the latter years of this review. What is clear from these data, however, is that routine use of the IMA did not in any way increase the incidence of major surgical complications. In particular, elderly patients with diabetes did not have a higher incidence of sternal wound infection after IMA harvesting.

Analysis of those patients who did not receive IMA grafts between 1986 and 1988, when IMA grafting in the elderly became "routine," indicates that some excluded patients were believed to be too unstable or too ill for the use of additional time required for IMA harvest before initiation of cardiopulmonary bypass. As noted in Table 5, however, the absolute number of these exclusions is quite small. In addition, other preoperative characteristics of the IMA group suggested a population at least as ill as the vein-graft-only patient group. The incidence of unstable angina was significantly greater in the IMA patients and measured ejection fraction for these patients was less, with the difference in left ventricular function between the two groups being statistically significant. On the other hand, more of the non-IMA patients required coronary care unit admission before operation. The higher percentage of preoperative intraaortic balloon pump placement in the non-IMA patients, 11.9% versus 5.5% for IMA patients, may be a time-related factor because preoperative balloon pump placement was more commonly used during the early years of this review. Present policy, especially in elderly patients, would be to undertake immediate coronary artery bypass grafting rather than risk peripheral vascular complications associated with intraaortic balloon pump placement.

Even if unmeasured predictor variables or unspecified selection biases may account for some differences in early outcome between the two groups of patients, it is unlikely that such factors would influence the differences in late survival between these two patient groups. In fact, recipients of IMA grafts had significantly better survival during the first 4 years after bypass grafting compared with that of patients with vein grafts only. The presence of an IMA graft in these patients was one of the independent predictors of this improved survival. The midterm survival achieved in these elderly patients was particularly gratifying because they as a group exhibited a higher incidence of risk factors for poor outcome, such as unstable angina and reduced ejection fraction. An 86% actuarial survival for these patients at 4 years compared with 77% survival in elderly patients receiving only vein grafts is a dramatic outcome difference.

In summary, the results of this review appear to support the policy of routine LIMA grafting in patients older than 70 years who require coronary bypass grafting. Exclusion from IMA grafting based on the presence of diabetes does not appear to be warranted by the results of this study. Although elderly patients requiring bypass grafting clearly are at increased risk of operative death and surgical complications compared with younger patients, the presence of an LIMA graft appears to afford both improved early and late survival.

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DISCUSSION

DR H. STORM FLOTEN (Portland, OR): The general theme of this report is that increased age should not be a deterrent to the use of LIMA as a conduit for coronary bypass grafting. We in Portland agree with this basic concept and have data that closely resemble those of the Johns Hopkins group.

In a 4-year period, 1984 to 1988, we had over a thousand patients older than 70 years receiving coronary bypass grafts. Only one third of our patients, however, received an IMA graft. Almost all the preoperative and postoperative variables coincide with the findings of the Hopkins group, and we also show a significantly lower operative mortality of 3% in the LIMA group versus 8% in the non-LIMA group.

In 1984, we very sparingly used the LIMA in patients older than 70 years. In 1988, 50% of our patients received LIMA grafts; however, this is not nearly as high a percentage as in the Hopkins group. More recently, we have adopted the same philosophy of routine use of the LIMA as the Hopkins group.

Actuarial survival out to 4 years almost exactly corresponds with the Hopkins patient population. The 1% to 2% better survival in Portland must be due to the fresh air and abundance of fine drinking water in the great Northwest.

I have difficulty advocating a cause and effect relationship between the use of LIMA and decreased operative mortality. To say that the improved operative mortality is a consequence of the use of the LIMA, we would need to show that the operative mortality was primarily related to vein graft closure. This leads to the question: are the two groups comparable? Not according to time frame, as 80% of the LIMA grafting was done after 1986 and 90% of the vein grafting before 1986. To some degree, at Hopkins and in our series, we selected out the patients, as shown by the fact that 12% of the vein graft patients received intraaortic balloon pump preoperatively versus 5.5% for the LIMA patients. Other characteristics that differ between the groups are the percentage of patients in intensive care preoperatively and the number of grafts performed.

It will be some time yet before we can look at the long-term survival in the subset of patients because 80% of LIMA graft operations were done after 1986.

I pose three questions. Was the cause of operative death investigated in these patients? Could you please comment on the reason for an increased incidence of stroke in the non-LIMA patients? Presuming that the LIMA and non-LIMA groups are comparable, how do you explain the statistically lower operative mortality in the LIMA group?

We in Portland agree with the concept that LIMA use in the group older than 70 years does not increase the morbidity or mortality for coronary bypass grafting in these patients.

DR ANTHONY J. ACINAPURA (New York, NY): As you know, we are all seeing an increasing number of patients 70 years of age or older who need coronary bypass grafting. A recent review of our bypass cases over the past 10 years show that 24% or 1,385 patients were 70 years of age or older. The number of patients in this age group who undergo coronary bypass grafting is increasing rapidly to the point where 38% of our bypass cases in 1988 were in patients 70 years of age or older. Currently our average age for bypass grafting is 68 years. This subset of patients certainly represents a high-risk group, with an operative mortality, as we reported at the American Heart Association meeting 2 years ago, of 8%.

Due to earlier reports of increased patency, we began using the IMA as our conduit of choice for grafting to the anterior descending coronary artery in 1984. Two years ago, at our Society meeting, we presented data showing increased survival in patients with IMA grafts to the anterior descending coronary artery compared with patients with saphenous vein grafts. If we look at actuarial survival, we see a 90% survival with the IMA at 9 years compared with 78% with the saphenous vein graft. There was also a statistically significant decreased incidence of recurrent angina, myocardial infarction, and reoperative coronary artery bypass grafting in the IMA group. Accordingly, the IMA is used in 90% of our patients regardless of age, and we have not seen any increased morbidity with IMA usage.

When we looked at the survival curves of patients 70 years of age or older and those younger than 70 years, we saw no difference if the hospital mortality is excluded. This attests to the appropriateness of IMA bypass grafting in this high-risk group of patients and supports Dr Gardner's conclusions that the LIMA graft to the anterior descending coronary artery, due to its increased patency, appears to increase longevity and probably will decrease the need for reoperative coronary artery bypass in this elderly subset of patients.

DR HOSSEIN NARAGHIPOUR (Cleveland, OH): In St. Vincent's Charity Hospital in Cleveland, we have been using the IMA for bypassing the coronary arteries since December 1969. In 1974, before this Society, I reported the long-term patency rate of the IMA bypass graft. At that time I was convinced of the advantages of IMA grafts over vein grafts.

We have perfected the sternal retractor that we used at that time. It was initially made in our hospital and is now being manufactured by Pemco in Cleveland and commercially available. It is a great tool for dissection and exposure of the IMA.

Since the early times, my associates and I have done more than 10,000 IMA bypass operations for myocardial revascularization. I would like to point out a few important points that we have learned in the past almost 20 years.

There must be always a critical stenosis of coronary arteries for the IMA to take over the circulation of the coronary artery. This means the stenosis should be more than 70%. All branches of coronary arteries can be bypassed by the IMA graft. The LIMA can be used for bypass in all the branches of the left coronary artery. The right IMA can be used for bypass in the right coronary artery, right posterior descending, left anterior descending, diagonal, and occasionally the lateral branch of the circumflex coronary artery. The free IMA grafts can be used for any branches of the coronary artery.

The patency rate of the IMA is very impressive, around 97% in most centers. Failures are early and technical, and depend on how the IMA is dissected and used for anastomosis. We have not seen a patent IMA fail or occlude like the vein graft later unless the progression of the arteriosclerosis of coronary arteries interferes with the functioning of the IMAs. The IMA graft can be used in patients of any age or sex. You never know how it is anatomically unless it is dissected or explored.

Internal mammary artery grafts can be used in emergency cases, after failure of percutaneous transluminal coronary angioplasty, and for reoperation. If the patient's condition is stable, we dissect the IMA as in a routine case. Patients whose condition is unstable are put on cardiopulmonary bypass before the IMA is dissected.

The IMA graft is able to adapt its flow as time goes on, and as stenosis of recipient artery progresses, the IMA grafts all get larger.

DR ROBERT A. GUYTON (Atlanta, GA): I enjoyed the discussion and I agree with the conclusion. However, I must say that I do think that it is more difficult to maintain optimal myocardial protection with the IMA graft, particularly in patients with extremely bad ventricles. I note that in this report the vein graft group had a significantly greater proportion of patients requiring an intensive care unit preoperatively and a significantly greater proportion of patients requiring internal aortic balloon pump preoperatively, yet the IMA group had a significantly higher need for catecholamines postoperatively. Does this not suggest that it was more difficult to protect the heart intraoperatively with the use of the IMA graft?

DR GARDNER: I would like to thank all of the discussants for their comments and for reviewing their clinical data, which, we believe, support our conclusion that the IMA graft is appropriate for elderly patients.

Dr Floten, I am unable to explain the difference in operative mortality rates between our two groups of elderly patients. I note that your operative mortality rates were likewise different, but were quite similar to those that I have just reported. We had expected to be able to establish the fact that cardiac causes of death might have been fewer in patients receiving IMA grafts, assuming that even early patency of the IMA graft is better than for vein grafts. With relatively few patient deaths, however, we were unable to establish any differences in the causes of death between the two patient groups.

With respect to the higher incidence of intraaortic balloon pump usage in the vein graft patients, I believe that the explanation for this is a difference in philosophy toward balloon pump use during the early 1980s compared with more recently. We rarely use the balloon pump now in elderly patients, preferring instead to take the patient directly to the operating room if and when he or she becomes unstable, rather than attempting to stabilize the patient with a period of balloon counterpulsation. We are concerned about peripheral vascular complications associated with balloon pump usage in the elderly patient and try, therefore, to avoid insertion of the intraaortic balloon catheter.

Dr Guyton, your comments reflect your usual keen critical insight. I do believe, however, that our current policy toward inotropic drug use postoperatively is somewhat more liberal than was our policy in the early years of this review and does not reflect less good myocardial protection in patients receiving IMA grafts. We currently rely more on topical myocardial cooling than on reinfusion cardioplegic techniques. Your suggestion that myocardial protection in IMA patients may be less effective is an intriguing one and deserves further attention.

Seventeen-Year Experience With Bilateral Internal Mammary Artery Grafts

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The internal mammary artery (IMA) is being recognized as the conduit of choice for myocardial revascularization. From January 1972 through June 1988, 1,087 patients received bilateral IMA and supplemental vein grafts. There were 917 men (84.4%) and 170 women (15.6%) with a mean age of 62.4 years (range, 29 to 84 years). Three hundred ninety-four patients (36.2%) had unstable angina, and 194 (17.8%) had left main coronary artery stenosis greater than 50%. In all, 3,741 coronary grafts were performed, with a mean of 3.4 per patient. Hospital mortality was 2.7% (29 patients). Hospital complications included reoperation for bleeding, 19 patients (1.7%); sternal infection, 16 patients (1.5%); respiratory failure, 35 patients (3.2%); perioperative myocardial infarction, 22 patients (2.0%); and stroke, 20 patients (1.8%). Postoperative arteriography in 53 patients (mean postoperative time, 53.0 months) showed that 92.1% (58/63) of the left IMA and 84.9% (45/53) of the right IMA grafts were patent. Follow-up was completed on 1,058 hospital survivors. There were 82 late deaths (7.8%). The actuarial survival for patients discharged from the hospital was 80.0% ± 3.2% (plus or minus standard error of the mean) at 10 years and 60.0% ± 5.0% at 15 years. At follow-up, 866 patients (90.3%) were asymptomatic and in New York Heart Association class I and 68 (7.1%) were in class II. This longitudinal analysis demonstrates that bilateral IMA grafting has a low operative risk and provides excellent long-term functional improvement and survival.

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There is growing recognition that the success of myocardial revascularization depends on graft patency and the rate of progression of the intrinsic coronary artery disease. Studies have shown that the internal mammary artery (IMA) graft has superior early and long-term patency as compared with the saphenous vein [1–5]. Patients receiving a left IMA graft to the anterior wall as compared with the saphenous vein have had improved long-term survival and a reduction in the rate of reoperation and late cardiac events [6, 7]. Methods to extend the use of this preferred conduit have included bilateral, free, and sequential grafts [3, 4, 8–12].

In 1985, we reported a 12.5-year experience with bilateral IMA grafts in 227 patients. This study demonstrated a low operative risk and excellent long-term results [8]. Routine use of bilateral IMA grafts remains controversial, however [13]. The surgical community has voiced concern that this complex and often technically demanding procedure may increase the patient's operative risk. Moreover, the efficacy of bilateral IMA grafts in patients with unstable angina, left main coronary artery disease, and reduced left ventricular function has not been clearly established.

Assessing superior, long-term results in patients with bilateral as compared with single IMA grafts is difficult due to differences in patient populations and the duration of available follow-up data. We present a retrospective analysis of our 17-year experience with 1,087 patients receiving bilateral IMA grafts.

Material and Methods

Patient Population

From January 1972 through June 1988, 1,087 patients underwent primary coronary revascularization of the myocardium with bilateral IMA and supplemental vein grafts. This patient group represents 35.0% of our entire patient population receiving coronary bypass grafts during the reporting interval. In recent years, the annual distribution of bilateral IMA grafts has continued to increase (Fig 1). In the present series, there were 917 men (84.4%) and 170 women (15.6%) ranging in age from 29 to 84 years. The mean age for the group was 62.4 years. Since the inception of the study, the mean age has increased significantly ($p < 0.05$). During the period between January 1972 and December 1981, the mean age was 51.6 years; between January 1982 and December 1984, the mean age was 59.9 years; and, more recently, between January 1985 and June 1988, the mean age increased to 64.1 years.

Coronary risk factors in the series included hypertension (diastolic pressure greater than 90 mm Hg) in 498 patients (45.8%), hyperlipidemia in 186 patients (17.1%), diabetes in 222 patients (20.4%), smoking in 614 patients (56.4%), positive family history in 601 patients (55.2%), and previous myocardial infarction in 540 patients (49.6%). The incidence of risk factors has remained relatively constant over the last 6 years. The patients' pre-

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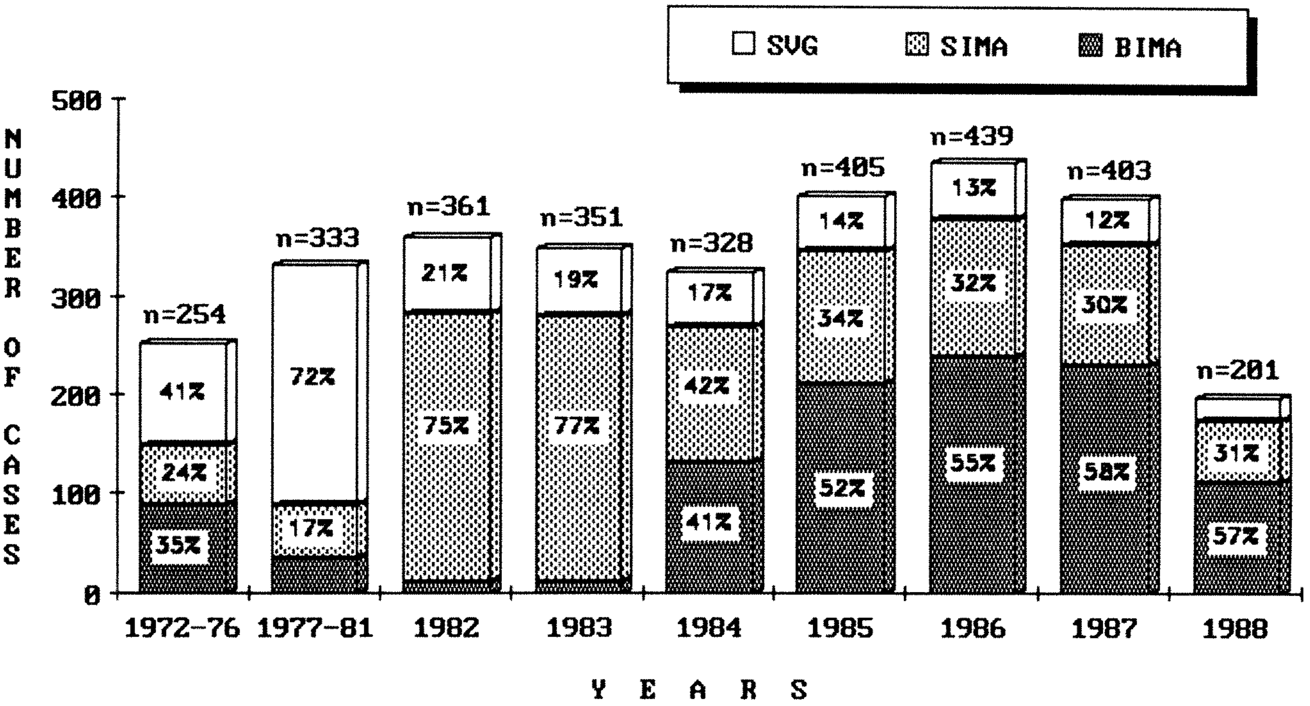

Fig 1. Annual distribution of primary coronary bypass grafting (1988 includes cases between January and June only). (BIMA = *bilateral internal mammary artery;* SIMA = *single internal mammary artery;* SVG = *saphenous vein graft.)*

operative symptoms were defined by the New York Heart Association (NYHA) classification [14]. Fourteen patients (1.2%) were in class I, 125 (11.4%) were in class II, 554 (50.9%) were in class III, and 394 (36.2%) were in class IV. Unstable patients comprised the group with class IV symptomatology.

Preoperative angiography demonstrated triple-vessel disease in 804 patients (74.0%) and double-vessel disease in the remaining 283 patients (26.0%). Left main coronary artery disease (greater than 50% stenosis) was present in 194 patients (17.8%). Ejection fraction determination from left ventriculography was performed in 1,009 patients. Of this group, the ejection fraction was greater than 50% in 736 patients (67.7%), between 30% and 50% in 232 patients (21.3%), and less than 30% in 41 patients (3.8%). The ejection fraction was unavailable in 78 patients (7.2%) in the series.

In all, 3,741 coronary grafts were performed, with an average of 3.4 grafts per patient. Each patient in the series received bilateral IMA grafts, and in 824 patients (75.8%) an additional 1,198 grafts were constructed with autologous vein. The type of conduit and corresponding recipient arteries are shown in Table 1. There were 340 sequential left IMA and 29 sequential right IMA grafts. The right IMA was placed through the transverse sinus and grafted to the circumflex or obtuse marginal artery in 531 patients (48.9%). Eight left IMA and 34 right IMA conduits were used as free grafts.

Operative Technique

The IMAs were exposed through a standard median sternotomy incision using an Ankeney or Pittman retractor. Isolation from the adjoining vein and fascia was achieved with low-voltage electrocoagulation to avoid thermal damage to the arterial wall and phrenic nerve proximally. The IMA was mobilized from the origin to beyond its bifurcation. After heparinization, the distal branches were divided, clipped, and wrapped with a papaverine-soaked sponge (60 mg/30 mL of saline solution). Patients in unstable condition were routinely heparinized immediately after sternotomy and before mobilization of the IMA conduits. Free flow was assessed grossly, and if it was reduced due to vasospasm, correction was obtained with use of an intraluminal No. 2 or 3 Fogarty catheter sprayed with dilute papaverine solution. Serious intramural injury with impaired flow forced abandonment of the arterial graft. The IMA grafts were brought into the pericardial sac medial to the apical pleura and posterior to the thymus gland through strategically placed pericardial windows to enhance length, prevent torsion, and reduce tension. Coronary anastomosis was performed with continuous 7-0 or 8-0 Prolene suture (Ethicon, Somerville, NJ) using optical magnification dur-

Table 1. Coronary Arteries Grafted and Type of Conduits

Conduit	LAD	DIAG	CX	RCA/PDA	Total
Left IMA	947	320	151	9	1,427[a]
Right IMA	100	79	548	389	1,116[b]
Vein	74	72	459	593	1,198
Total					3,741

[a] Includes 340 sequential and eight free grafts. [b] Includes 29 sequential plus 34 free grafts, and 531 grafts through the transverse sinus.

CX = circumflex coronary artery; DIAG = diagonal coronary artery; IMA = internal mammary artery; LAD = left anterior descending coronary artery; PDA = posterior descending artery; RCA = right coronary artery.

ing hypothermic (28° to 32°C) cardiopulmonary bypass. Since 1978, myocardial protection during aortic cross-clamping has included topical cooling and antegrade cold (4° to 5°C) blood cardioplegia repeated every 20 minutes to maintain the septal temperature between 10° and 15°C. Retrograde coronary sinus cardioplegia has been used in patients with aortic valve incompetence or severe left main coronary artery stenosis since 1988. In most patients, aortic root venting was also used. Mean cardiopulmonary bypass time for the series was 118.04 ± 41.11 minutes (range, 25 to 422 minutes), and the mean duration of aortic cross-clamping was 71.41 ± 0.89 minutes (range, 0 to 185 minutes).

Follow-up

Perioperative data were obtained from the patient's hospital record. Follow-up information was collected yearly or more frequently as necessary through direct patient contact, from the patient's personal physician, from responses to mailed questionnaires, or by telephone interview with surviving patients or family members. When patients were difficult to locate, the services of Equifax of McLean, VA, were used to secure the required follow-up data. Data collected were entered into a computer-assisted reporting system. Two computer-compatible data collection instruments—a patient registration form and a follow-up form—were completed for each patient. These data collection instruments provided standardized reporting of each patient's clinical status preoperatively and postoperatively.

Statistical Methods

Data are presented in the text and tables as simple percentage and frequency distributions. Values of continuous variables are expressed as the mean ± the standard deviation. Comparison of means for continuous variables was conducted using an unpaired Student's t test. Significance of differences in discrete variables was evaluated using χ^2 analysis. Patient survival is expressed by actuarial analysis according to the method of Kaplan and Meier [15] and by linearized occurrence rates. Data collected were subjected to both quantitative and qualitative analysis with the aid of the Patient Analysis and Tracking System software [16]. Differences resulting in a p value of less than 0.05 were considered significant.

Results

Mortality

The hospital mortality for the series was 2.7% (29 patients). A significant difference ($p < 0.005$) in hospital mortality was observed when stable and unstable patients were compared. The presence of left main coronary artery disease or impaired left ventricular function did not have a significant influence on hospital mortality.

Hospital Complications

The reported hospital complications included reoperation for bleeding, sternal infection, respiratory failure with intubation for more than 48 hours and tracheostomy, perioperative myocardial infarction, and stroke (Table 2). The incidence of postoperative morbidity for the series was low, with most patients ($n = 1,000$; 92.0%) experiencing no hospital complications.

Table 2. Hospital Complications

Complication	No.[a]
Bleeding requiring reoperation	19 (1.7)
Sternal infection	16 (1.5)
Respiratory failure	
Intubation >48 hours	23 (2.1)
Tracheostomy	12 (1.1)
Perioperative myocardial infarction	22 (2.0)
Stroke	20 (1.8)

[a] Numbers in parentheses are percentages.

A statistically significant ($p < 0.005$) higher incidence of sternal infection was reported in diabetic patients. The incidence of sternal infection was not affected by the patients' age or sex, however.

Late Cardiac Events

The linearized occurrence rate and number of late cardiac events in 959 survivors were as follows: nonfatal myocardial infarction, 1.18% per patient-year (40 events); reoperation for coronary artery disease, 0.27% per patient-year (nine events); and percutaneous transluminal coronary angioplasty, 0.21% per patient year (seven events).

Long-Term Follow-up

Follow-up data were collected for 1,041 of 1,058 patients discharged from the hospital. Seventeen patients (1.6%) were lost to follow-up in the series. The follow-up period ranged from 1 to 17 years with a mean of 3.26 years. The cumulative follow-up for the series was 3,393.7 years. The linearized late mortality rate for the series was 2.42% per patient-year (82 events).

At the completion of the current follow-up, 959 (90.6%) of the hospital survivors were alive. The status of patients and causes of late deaths are shown in Table 3.

The survival data for 1,058 patients discharged from the hospital are shown in Figure 2. At 10 years, survival was 80.0% ± 3.2% (± the standard error of the mean); at 17 years, survival was 56.2% ± 5.9%.

Table 3. Current Status of Hospital Survivors

Status	No.[a]
Alive	959 (90.6)
Lost to follow-up	17 (1.6)
Dead	
Cardiac related	34 (3.2)
Noncardiac related	27 (2.6)
Cause unknown	21 (2.0)
Total	1,058

[a] Numbers in parentheses are percentages.

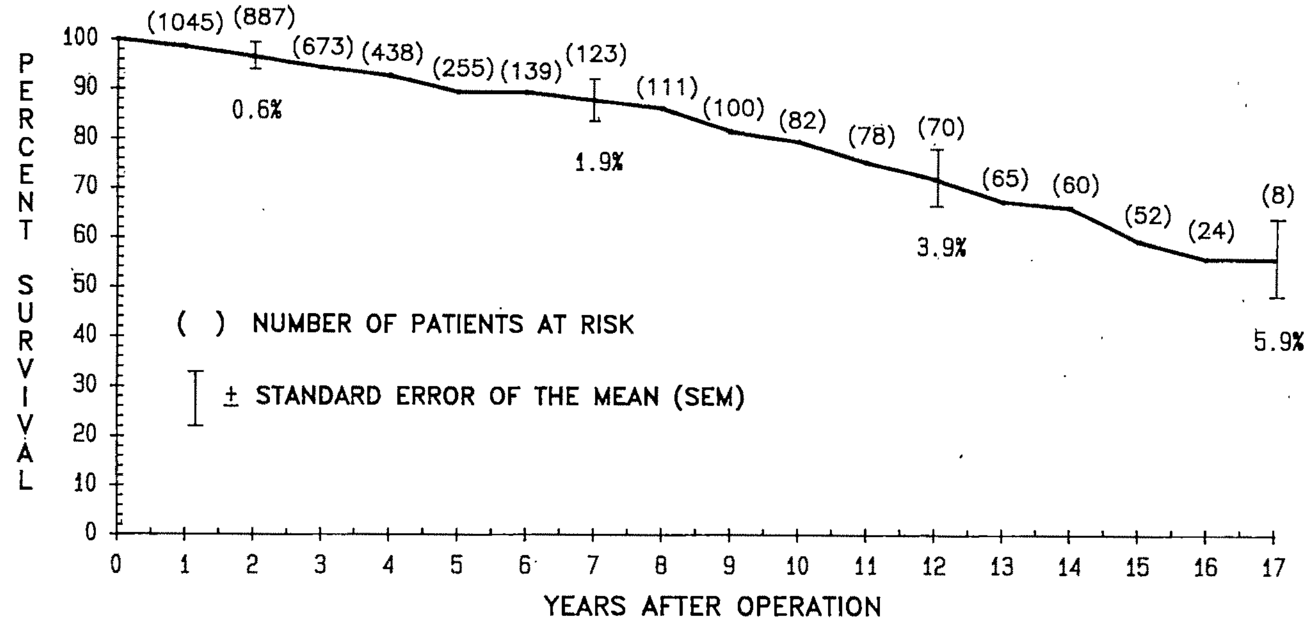

Fig 2. Actuarial survival of patients discharged from the hospital.

Table 4 shows the NYHA classification for all surviving patients by follow-up interval. At follow-up, 866 patients (90.6%) were asymptomatic and in NYHA class I. Of patients experiencing angina, 68 (7.1%) were in class II, 19 (2.0%) were in class III, and 6 (0.6%) were in class IV.

A subsample of the patient population in this study was comprised of the first 89 patients who underwent myocardial revascularization between 1972 and 1975. Follow-up was completed in 83 of 85 hospital survivors (97.6%). Two patients (2.4%) were lost to follow-up. The follow-up period extended from 4.5 to 17 years (mean, 13.2 years). The cumulative follow-up for this subsample of long-term survivors was 1,095.6 years. The linearized mortality rate for this group was 2.46% per patient-year. The etiological process of the 27 late deaths showed that 10 (37.0%) were cardiac related and 9 (33.3%) were noncardiac related; in 8 patients (29.6%), the cause of death was unknown.

Late cardiac events were documented in 56 long-term survivors (65.4%). Myocardial infarction was reported in 11 patients (19.6%), reoperation was performed in 2 patients (3.5%), and percutaneous transluminal coronary angioplasty was performed in 1 patient (1.7%). At the current follow-up, 42 patients (75.0%) were asymptomatic and in NYHA class I. Of patients experiencing angina, 12 (21.4%) were in NYHA class II and 2 (3.6%) were in class III (Table 4).

Table 4. New York Heart Association Functional Class in 959 Survivors Based on Follow-up Time Interval

Follow-up Interval (yr)	No.	NYHA Class[a]			
		I	II	III	IV
1–3	552	507 (91.8)	28 (5.0)	13 (2.3)	4 (0.7)
4–7	326	293 (89.8)	27 (8.2)	4 (1.2)	2 (0.5)
8–13	25	24 (96.0)	1 (4.0)	0 (0.0)	0 (0.0)
14–17	56	42 (75.0)	12 (21.4)	2 (3.5)	0 (0.0)

[a] Numbers in parentheses are percentages.

Graft Patency

During the follow-up period, 53 patients in the series underwent recatheterization from 2 months to 15 years postoperatively (mean postoperative time, 53.0 months) for recurrent chest pain suggestive of angina. Of the 63 left IMA anastomoses, 58 (92.1%) were patent. All 10 left IMA sequential grafts (100%) to the diagonal and the left anterior descending coronary artery were patent. Of 53 right IMA grafts, 45 (84.9%) were patent. Of the 49 vein grafts, 32 (65.3%) were patent. The patency of specific IMA coronary artery grafts is shown in Table 5.

Comment

The IMA is the conduit of choice in coronary bypass grafting. It has an early patency rate superior to that of vein grafts [4]. Long-term patency for IMA grafts has been reported to approximate 90% [1–3, 5]. In contrast, the rate of vein graft failure approaches 50% between 5 and 12 years, largely due to development of graft atherosclerosis [2, 3, 5]. The relative immunity from atherosclerosis of the native IMA persists when it is used as a coronary graft [17]. The IMA graft has been observed in sequential angiographic studies to increase in size as dictated by myocardial blood demand [5]. These characteristics contributed to enhance survival and reduce the incidence of late cardiac events and reoperation in patients who received left IMA grafts as compared with those who received only vein conduits [6, 7].

Recently, reports with favorable early results of complex mammary artery grafting including bilateral and sequential techniques have appeared in an effort to expand use of this preferred conduit [4, 9, 10]. After an

Table 5. Postoperative Arteriography of Bilateral Internal Mammary Artery Grafts in 53 Patients at a Mean Interval of 53.0 Months

Graft site	No. of Grafts	No. Patent[a]
Left IMA		
LAD	31	28 (90.3)
DIAG/LAD	20	20 (100.0)
OM	11	10 (90.9)
DIAG	1	0 (0.0)
Total	63	58 (92.1)
Right IMA		
RCA/PDA	22	19 (86.3)
LAD	11	10 (90.9)
DIAG	3	2 (66.6)
OMB	17	14 (82.3)
Total	53	45 (84.9)

[a] Numbers in parentheses are percentages.

IMA = internal mammary artery; DIAG = diagonal coronary artery; LAD = left anterior descending coronary artery; OM = obtuse marginal branch; PDA = posterior descending artery; RCA = right coronary artery.

earlier report in 1985 [8], we have used these techniques in almost 60% of the patients receiving coronary bypass grafts.

The IMA has been most commonly mobilized as a pedicle [3, 4, 9–18]. Techniques to maximize length and avoid tension have included multiple fasciotomies in the pedicle, division of the internal mammary vein at its subclavian origin, and mobilization of the pedicle into its distal bifurcation [18].

In our patient group, the IMA has been isolated, independent of the endothoracic fascia, internal mammary veins, and lymphatics. Although the risk of IMA injury during mobilization may be greater, this method has several advantages. It permits visualization of the entire conduit to assure that no intramural hematoma or injury has occurred. Moreover, this techniques provides superior length. Whereas the pedicled right IMA has been criticized for inadequate length [3, 9], the in situ isolated right IMA commonly reaches the distal right coronary, posterior descending, and obtuse marginal arteries. We prefer placing the right IMA through the transverse sinus to revascularize the circumflex artery because this is the shortest route [19]. This approach protects the right IMA conduit from injury in the event of reoperation. In addition, the isolated right IMA in a retroaortic position may be less susceptible to compression than a pedicled graft. The isolated IMA conduit facilitates construction and appropriate orientation of sequential grafts.

In this study, the documented late patency rates of the left IMA (92.1%) and right IMA (84.9%) as compared with the saphenous vein (65.3%) are similar to those described in other reports [1, 3, 5] and confirm the efficacy of the isolated IMA graft. All 20 anastomoses in the 10 sequential left IMA to diagonal and left anterior descending coronary artery grafts restudied were patent. Fourteen of 17 right IMA grafts (82.3%) placed through the transverse sinus to revascularize the circumflex artery were patent.

Our experience has shown that hospital mortality is not increased with bilateral IMA grafting. Some reports have suggested limiting the bilateral IMA procedure to clinically stable male patients with good ventricular function [3, 10]. Our experience with a hospital mortality of 2.7% (29/1,087 patients) includes a heterogenous population. In patients in stable condition, the hospital mortality of 1.2% (8/693) compares favorably with 1.4% in patients with mild angina randomized to operative therapy in the Coronary Artery Surgery Study [20]. The 5.3% (21/394) hospital mortality for patients with unstable angina is similar to that of recent reports, in which it ranged from 3.9% to 8.5% [21, 22]. Although in previous studies left ventricular dysfunction was shown to increase hospital mortality [21, 23], in our experience patients with moderate impairment of ejection fraction (35% to 50%) had hospital mortality similar to that of patients with normal ventricular function. Although hospital mortality increased in patients with profound left ventricular dysfunction (ejection fraction less than 35%), it did not achieve statistical significance.

Left main coronary artery stenosis (more than 50%) has been reported in some studies to influence hospital mortality [24, 25]. In other studies, it was not a contributing risk factor [26, 27]. Although application of the left IMA in patients with left main coronary artery disease has proved favorable, use of bilateral IMA grafts in this category of patients has rarely been addressed. In this series, bilateral IMA grafting was accomplished safely in 194 patients (17.8%) with left main coronary artery disease. The hospital mortality was 2.0%, not statistically different from that of patients without left main coronary artery disease.

Some reports have expressed concern that postoperative complications increase with bilateral IMA grafting [13]. The additional dissection required for mobilization of both IMAs may increase the potential for postoperative bleeding. In this series, however, the 1.7% (19/1,087 patients) rate of reexploration for bleeding was low and comparable with that of other reports [9, 28]. Devascularization of the sternum was suggested as contributing to an 8.5% incidence of sternal wound infection in patients with bilateral IMA grafts [29]. Recently, a 2.4% incidence of sternal wound infection related more to diabetes and age than to bilateral IMA grafting. This occurrence was reported from a retrospective analysis of three computer-matched groups of patients receiving either veins only, one IMA graft, or two IMA grafts [28]. In our series, a rate of sternal wound infection of 1.5% (16/1,087 patients) was noted. Diabetes was a statistically significant risk factor influencing the rate of sternal infection.

The increased period of anesthesia before cardiopulmonary bypass required for mobilization of both IMAs may permit the occurrence of ischemia. In this series a 2.0% (22/1,087 patients) incidence of perioperative myocardial infarction (new onset of Q waves) is consistent with the incidences reported in other studies [4, 9, 28]. These results reflect sophistication in cardiac anesthesia and the ability of bilateral IMA conduits to deliver sufficient blood flow to meet myocardial demands. The incidence of respiratory failure and stroke in the current study was low and similar to that previously reported [9, 28].

The goals of any coronary revascularization procedure are to eliminate or ameliorate angina and prolong the patient's survival. In analyzing more than 20,000 patients revascularized primarily with vein grafts between 1970 and 1981, Hall and associates [30] reported a 10-year survival probability of 70%. Barner and associates [3] reported a 10-year actuarial survival of 84% in 1,000 patients receiving IMA and occasional vein grafts. In 103 patients, bilateral IMA grafts were used. Loop and associates [6] reported a 10-year actuarial survival of 82.5% in 1,249 patients with left IMA and occasional vein grafts as compared with 71.0% in 2,116 patients with vein grafts only. This latter population included primarily patients in stable condition with triple-vessel disease.

In the current series, the 10-year and 17-year actuarial survivals were 80% ± 3.2% and 56.2% ± 5.9, respectively. The mean age of this patient population was 62.4 years, as compared with 52 years in previously cited reports. Enhanced long-term survival in patients with bilateral IMA grafts as compared with patients with single left IMA grafts may be very difficult to evaluate. In most patients, the left IMA is used to revascularize the left anterior descending coronary artery. This vessel may be strategically more important than any other coronary artery except the left main. Prolonged patency of a left IMA to left anterior descending coronary artery graft with preservation of the anterior wall may be sufficient for extending longevity.

Recurrent angina in postoperative patients may be generated by any ischemic area of myocardium either from a closing vein graft or progression of native coronary artery atherosclerosis. Barner and associates [3], who included in their study patients with primarily single IMA and occasional vein grafts, reported that 42.2% had recurrent angina, 7.6% experienced late myocardial infarction, and 4.6% required reoperation or percutaneous transluminal coronary angioplasty during a mean follow-up period of 6.3 years. Loop and associates [15], comparing patients with left IMA grafts to patients with vein grafts only, reported no difference in the rate of recurrent angina. In 2,295 patients with left IMA grafts, 18.8% returned to NYHA functional class III or IV, 10.4% experienced late myocardial infarction, and 3.9% required reoperation at a mean follow-up period of 8.5 years.

In the current series, the majority of the hospital survivors (90.3%; 866/959) were asymptomatic and in NYHA class I and 7.1% (68/959) were in class II. Only 2.6% (25/959) returned to NYHA functional class III or IV. There was a low incidence of nonfatal myocardial infarction (4.2%; 40/959 survivors), reoperation (0.9%; 9/959 survivors), and percutaneous transluminal coronary angioplasty (0.7%; 7/959 survivors).

In the long-term group of 56 patients who were followed for a mean interval of 13.2 years, 42 patients (75.0%) were asymptomatic and in NYHA class I and 12 patients (21.4%) were in class II. Two patients (3.6%) experienced NYHA functional class III anginal symptoms. In this long-term group, 2 patients (3.6%) required reoperation and 1 patient (1.8%) underwent percutaneous transluminal coronary angioplasty. These excellent functional results and the low incidence of morbid events suggests the influence of superior patency in bilateral IMA grafts.

The results of this longitudinal analysis provide substantial evidence that the isolated IMA graft has excellent patency and facilitates multiple grafting of the coronary arteries. The results demonstrate that bilateral IMA grafts can be performed safely in patients with unstable angina, left ventricular dysfunction, and left main coronary artery disease. The incidence of hospital morbidity is low, with 92.0% of the patients experiencing no complications.

The results of this study clearly indicate that bilateral IMA usage provides excellent 17-year functional improvement and patient survival and should be considered the procedure of choice when coronary revascularization is undertaken. Bilateral IMA grafting is technically feasible and can furnish the required nutritional demands of multiple areas of the myocardium. It not only increases survival, but also reduces the return of angina and provides freedom from late cardiac events.

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DISCUSSION

DR BRUCE W. LYTLE (Cleveland, OH): A myriad of data accumulated over the last 20 years clearly indicates that the strategy of using the left IMA to graft the left anterior descending coronary artery produces superior long-term results and particularly superior long-term survival when compared with the use of vein grafts only. This question has been answered.

The issue now is whether or not bilateral IMA grafts improve the long-term results further when compared with single IMA grafting. The current answer to that question, even including the data presented at this meeting both in this paper and in others, has to be a resounding "maybe."

Galbut and associates have documented a late survival of 80% at 10 postoperative years. The 10-year survival of our patients at the Cleveland Clinic Foundation who received bilateral IMA grafts is about the same, and neither their data nor ours show at this point a survival that is significantly better than that for roughly comparable groups of patients who have received single IMA grafts. It is my belief that bilateral IMA grafting will produce better long-term survival, but at this point the data are not so compelling that they make that conclusion self-evident. In both the series of Galbut and associates and our series, relatively small numbers of patients have been followed for more than 10 years. It may be that as a larger number of patients is followed for longer intervals the advantages of bilateral IMA grafts may become more clear, but for now we are going to have to be patient and to allow longer postoperative follow-up to enlighten us.

In the interim we need to carefully analyze the retrospective data with attention to variables that might allow us to identify subsets of patients for whom the advantages or disadvantages of bilateral IMA grafting may be more obvious. That has been done for early risk. It is now clear that elderly diabetic patients are at increased risk of a wound complication if bilateral IMA grafts are used. And in regard to the long-term results, it is our opinion that coronary bypass grafting for young adults and patients with hyperlipidemias represent specific indications for bilateral IMA grafting because of the suboptimal long-term results of vein grafts in these patients.

My only question to Dr Galbut is whether he and his colleagues have been able to identify predictors of high-risk or low-risk subgroups in terms of the late results after bilateral IMA grafting.

DR GALBUT: Our thoughts are comparable with yours. It would be very nice to say that bilateral internal mammary artery grafts prolong survival. The information will probably become more apparent over the next several years. One difficulty is that the left anterior descending may be the most important coronary artery, and a single internal mammary artery graft to the left anterior descending coronary artery may be sufficient in most patients to extend longevity.

However, as we believe long-term patency determines long-term functional results, patients that have bilateral grafts may do better functionally. The results in our long-term group, which has been followed from 14 to 17 years with a very low incidence of reoperation or the need for percutaneous transluminal coronary angioplasty, and with 75% being asymptomatic, reflect this feeling. Regarding the question of identifying particular subsets of patients in whom we would have information about predictors of late results, I do not have a clear answer.

Results of Internal Thoracic Artery Grafting Over 15 Years: Single Versus Double Grafts

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One hundred consecutive patients who had coronary artery bypass grafting using both internal thoracic arteries (ITAs) and saphenous veins, operated on during a 3-year period between 1972 and 1975, have been compared retrospectively with a series of 100 patients operated on during the same period who had one ITA graft along with saphenous vein grafts. The two groups were similar with respect to age, sex, risk factors for coronary artery disease, angina class, extent of coronary artery disease, left ventricular function, number of coronary bypass grafts performed, and completeness of revascularization. Single ITA operative mortality was 2% and double ITA, 9% (p = NS). The mean follow-up of hospital survivors was 14.4 ± 2.7 years; all but 7 patients had follow-up for at least 10 years. At 13 years, the actuarial patency of the right ITA was 85% and the left ITA, 82%. These data strongly suggest a survival benefit for patients with double ITA grafts among hospital survivors (74% versus 59%; $p = 0.05$). Patients receiving two ITA grafts had a significant freedom from subsequent myocardial infarction (75% versus 59%, $p < 0.025$), recurrent angina pectoris (36% versus 27%, $p < 0.025$), and subsequent total ischemic events (32% versus 18%, $p < 0.01$). These data also suggest improved freedom from coronary artery interventional therapy (percutaneous transluminal coronary angioplasty and reoperation) when two ITA grafts were used. These results support the use of bilateral internal thoracic artery grafting in selected patients.

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Patients receiving one internal thoracic artery (ITA) graft to the left anterior descending coronary artery enjoy increased longevity and greater freedom from ischemic cardiac events (eg, myocardial infarction, cardiac reoperation, hospitalization for ischemic causes) than patients having saphenous vein grafts only [1].

Such observations have prompted surgeons to use both ITAs in patients with multivessel coronary artery disease requiring revascularization. Whether the addition of a second ITA graft confers greater clinical benefit than a single ITA graft is not established. Johnson and associates [2] have reported that there was no improvement in actuarial survival in patients undergoing revascularization with multiple ITA grafts as compared with patients with single ITA grafts. Recent work by Kirklin and co-workers [3] demonstrated improved actuarial survival only in patients in whom one ITA was employed along with saphenous veins.

The excellent long-term patency of the ITA suggests that the improved patient longevity associated with one ITA graft might be extended if two grafts were used in patients with multivessel coronary artery disease requiring revascularization. This retrospective study was undertaken to examine this hypothesis.

Material and Methods

Between January 1972 and December 1975, 835 patients underwent isolated myocardial revascularization at St. Louis University Medical Center. In 365 of these patients, ITA grafts were employed. From February 1972 through May 1974 one or both ITAs were used in consecutive patients, including 100 patients who had bilateral ITA grafting from June 1972 through May 1974 [4]. After May 1974, patients were selected for left ITA bypass on the basis of age (<60 years), left ventricular function (left ventricular score <15), and coronary anatomy (left anterior descending artery stenosis >70%) [5]. From the remaining 265 patients with one ITA graft, a control series of 100 patients was matched for major preoperative variables and comparison made of results over the 14 years. Ninety percent of these operations were performed by Dr Barner, and all patients receiving one or two ITA grafts were operated on consecutively between 1972 and 1975.

The medical records of hospital survivors in both cohorts were retrospectively analyzed. Epidemiologic variables recorded were age, sex, and the presence or absence of known risk factors for coronary artery disease including smoking, essential hypertension, and insulin-dependent diabetes mellitus. Items of the cardiac history noted were a history of previous myocardial infarction, congestive heart failure (as defined by both digoxin and diuretic use), and the severity of angina as graded according to the Canadian Cardiovascular Association Classification.

Cardiac catheterization findings included the number of diseased vessels (≥70% obstruction of luminal diameter in

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any plane on coronary angiography), left main coronary artery disease (≥50% obstruction), left ventricular function quantitated by left ventricular score (as developed by the Coronary Artery Surgery Study), and left ventricular end-diastolic pressure.

The operations were performed jointly by the St. Louis University faculty and surgical residents. Distal anastomoses were established during intermittent ischemic arrest. Myocardial protection consisted of topical iced Ringer's lactate supplemented with systemic hypothermia to 26°C. Proximal vein graft anastomoses were established during systemic warming after removal of the aortic cross-clamp. Left ventricular venting was not routinely used. Both ITAs were used in situ and sequential ITA grafts were not used. The left ITA was grafted to the left anterior descending coronary artery and the right ITA, to the right coronary artery in all 100 patients. In the 100 control patients, the ITA was grafted to the left anterior descending coronary artery in 97 patients and to the right coronary artery in 3 patients.

Operative variables recorded included the number of distal anastomoses and completeness of revascularization, which was defined as grafting to one or more branches of the major coronary arteries (anterior descending, large marginal circumflex, and right coronary arteries) in which 70% or greater obstruction existed. Operative mortality was defined as any death occurring during hospitalization or within 30 days of operation.

Follow-up information was obtained between December 1988 and August 1989. Clinical confirmation of survival and subsequent cardiac events was obtained by telephone interview with patients or their physicians. Reports of cardiac catheterization occurring during the follow-up period were reviewed to document graft patency. Data were collected regarding absolute survival and the occurrence of ischemic events including recurrent angina, myocardial infarction, and cardiac death defined as death from myocardial infarction, congestive heart failure, or any unexplained sudden death. Both the occurrence of these events and the interval from operation were recorded.

Data were analyzed using the Statview II statistical software package (Brainpower, Inc, Calabasas, CA). The χ^2 test was used to determine significance for discrete variables. Continuous variables were analyzed using Student's t tests. Values were expressed as a mean ± standard deviation unless otherwise specified.

The actuarial method of Berkson and Gage [6] was used to describe overall survival, graft patency, and freedom from ischemic events such as angina, myocardial infarction, and death. Differences between actuarial curves were determined using the Mantel-Haenszel analysis [7]. A p value of less than 0.05 was considered significant.

Results

The clinical profiles of the two groups of hospital survivors are summarized in Table 1. These two groups had no significant differences with regard to age, sex, cardiac risk factors, history of cardiac disease, or preoperative catheterization variables. The number of distal anastomoses performed and the proportion of patients who had complete revascularization were virtually identical.

Table 1. Clinical Profile of Hospital Survivors

Variable	Single IMA	Double IMA	p Value
Preoperative			
No. of patients	98	91	. . .
Age	51.3 ± 6.6	49.6 ± 7.9	NS
Male sex (%)	85 (87)	76 (83)	NS
Smoking history (%)	75 (78)	68 (76)	NS
Diabetes mellitus (%)	3 (3)	4 (4)	NS
Essential HTN (%)	25 (26)	13 (15)	NS
Prior MI (%)	38 (39)	45 (50)	NS
History of CHF (%)	11 (13)	10 (13)	NS
Angina class	2.9 ± 1.0	3.1 ± 0.9	NS
No. of diseased vessels	2.5 ± 0.7	2.4 ± 0.6	NS
LV score	7.6 ± 2.7	7.6 ± 2.6	NS
LVEDP (mm Hg)	8.3 ± 5.0	8.5 ± 2.5	NS
Operative			
No. of distal anastomoses	2.3 ± 0.8	2.4 ± 0.5	NS
Complete revascularization (%)	70 (71)	63 (69)	NS

CHF = congestive heart failure; HTN = hypertension; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction.

The operative mortality was 2% in the single ITA group and 9% in the double ITA group (p = NS). The 2 patients with single ITA grafts died of postoperative mediastinal bleeding (1 patient) and acute subendocardial myocardial infarction (1 patient). The causes of death in the 9 patients who had double ITA grafts were acute subendocardial infarction (4 patients), sepsis with multiple organ system failure (3 patients), ventricular fibrillation (1 patient), and mediastinal bleeding (1 patient).

Follow-up for at least 10 years was obtained in all but 2 patients in the single ITA group (alive and lost to follow-up at 1 and 2.5 years) and 5 patients in the double ITA group (alive and lost to follow-up at 2.0, 8.2, 8.6, 8.8, and 9.3 years). The mean follow-up period was 14.3 ± 2.7 years for survivors with one ITA graft and 14.4 ± 2.7 years for survivors with two ITA grafts.

Survival

Analysis of the actuarial curves for hospital survivors strongly suggests a survival benefit for the presence of a second ITA graft ($p = 0.05$). The 10-year actuarial survival rates were nearly identical with values of 82% and 84% for patients with single and double ITA grafts, respectively. The curves diverge somewhat after 10 years with double ITA patients developing an advantage at 15 years (74% versus 59%, Fig 1).

Myocardial Infarction Recurrence

There was a significant difference in the actuarial freedom from myocardial infarction between the single ITA and double ITA groups ($p < 0.025$, Fig 2). The curves nearly

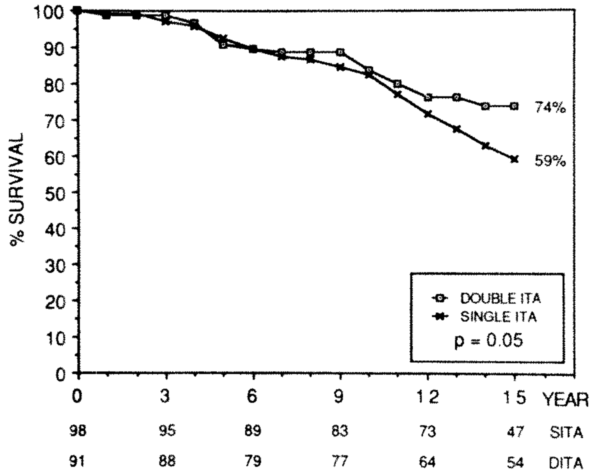

Fig 1. Actuarial survival of patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. Number of patients entering each interval is indicated beneath the abscissa.

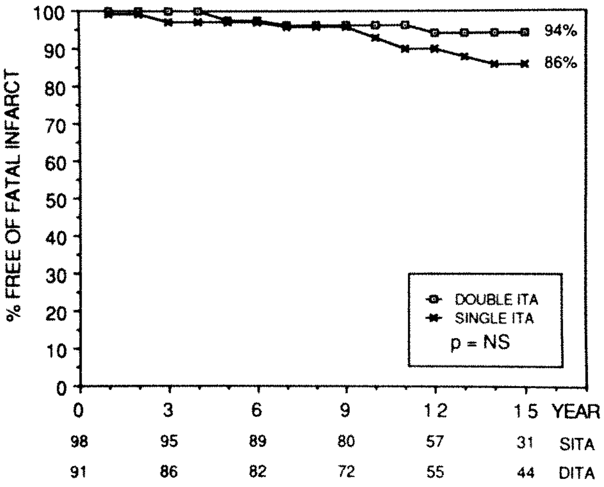

Fig 3. Actuarial freedom from fatal myocardial infarction of patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

overlap throughout the first 10 years and then separate. At 15 years, the freedom from myocardial infarction is 59% and 75% in patients with single ITA and double ITA grafts, respectively.

When myocardial infarction was categorized as fatal or nonfatal, there was a suggestion that patients with double ITA grafts might be afforded greater protection from both types of infarction (Figs 3, 4). However, these differences were not significant, perhaps because of the smaller number of patients available for analysis in either group.

Angina Pectoris Recurrence

Although angina pectoris recurred in the majority of patients in both groups at 15 years (single ITA group, 73%; double ITA group, 64%) (Fig 5), patients receiving two ITA grafts enjoyed greater freedom from angina pectoris recurrence throughout the 15-year follow-up ($p < 0.01$).

Freedom From Ischemic Events

When the two groups were compared for freedom from all ischemic cardiac events (angina pectoris, myocardial infarction, sudden unexplained death), the double ITA grafts conferred greater protection ($p < 0.01$) as shown in Figure 6. The frequency of reoperation tended to be greater in the group receiving a single ITA graft, but the difference did not achieve significance (single ITA, 13.4% versus double ITA, 11.0%; p = NS). Patients with two ITA grafts required percutaneous transluminal coronary angioplasty less frequently at any time in the postoperative period (single ITA, 11.3% versus double ITA, 3.3%; p = NS). When the needs for coronary angioplasty or reoperation were combined, there was no difference between groups (Fig 7).

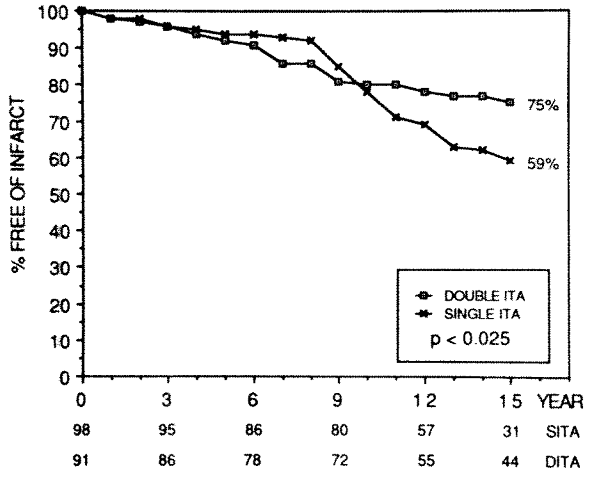

Fig 2. Actuarial freedom from recurrent myocardial infarction in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

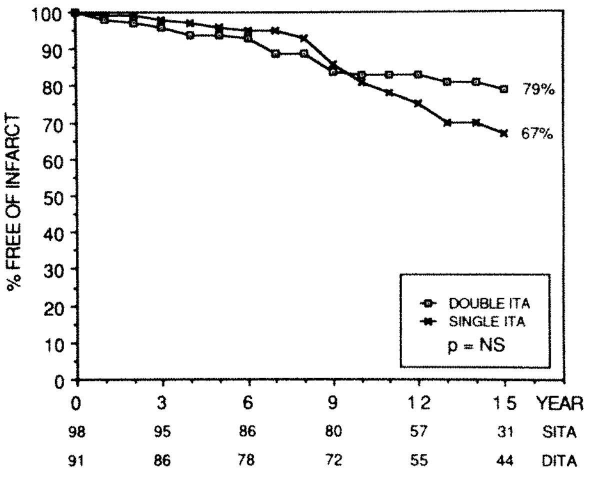

Fig 4. Actuarial freedom from nonfatal myocardial infarction in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

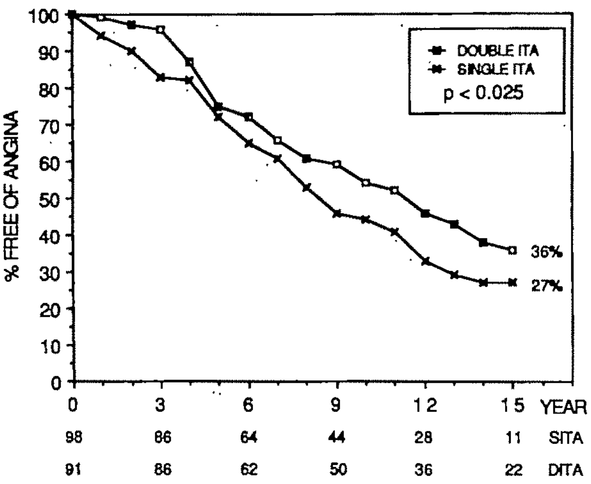

Fig 5. Actuarial freedom from recurrent angina pectoris in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

Patency

Among the 189 hospital survivors, 182 patients (96.3%) underwent at least one postoperative cardiac catheterization at a mean of 4.2 years postoperatively. Patients undergoing repeat catheterization beyond 5 years did so because of symptoms of myocardial ischemia or infarction.

The cumulative 13-year patency rate was 82% for the left ITA grafts and 85% for the right ITA grafts (p = NS) (Fig 8). There were no significant differences in the actuarial vein graft patencies in patients receiving one or two ITA grafts. The attrition rate of saphenous vein grafts approached 70% by the 12th postoperative year (Fig 9).

The actuarial patency of the internal thoracic artery in the double and single ITA groups was not significantly different (Fig 10).

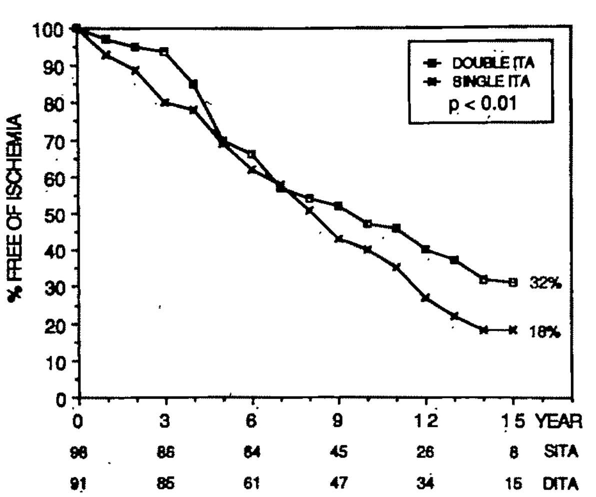

Fig 6. Actuarial freedom from all ischemic events in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

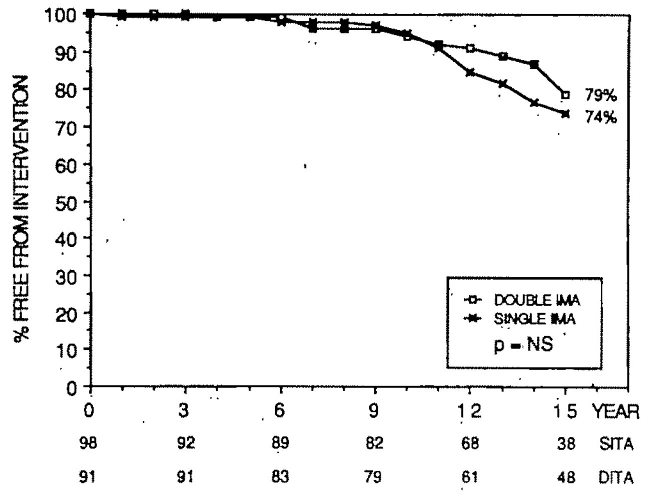

Fig 7. Actuarial freedom from intervention (percutaneous transluminal coronary angioplasty and reoperation) in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of patients entering each interval is indicated beneath the abscissa.

Comment

The clinical use of the ITA in the treatment of coronary artery disease was pioneered by George Green and associates beginning in 1968 [8]. Dr Barner began using one or two ITA grafts for myocardial revascularization in 1972 although the value of the ITA graft was not universally acknowledged at that time. Many surgeons questioned whether an ITA graft could provide enough flow to relieve ischemia, especially in patients with hypertrophied ventricles and large coronary arteries. In addition, early reports on the use of bilateral ITA grafting evidenced high rates of cardiac, respiratory, bleeding, and wound complications, causing many surgeons to discontinue its use [9]. Our own operative mortality of 9% for bilateral ITA grafting, although not dissimilar from other reports of that time, caused us to revert to the use of a single ITA graft [10]. The majority of surgeons never adapted the use

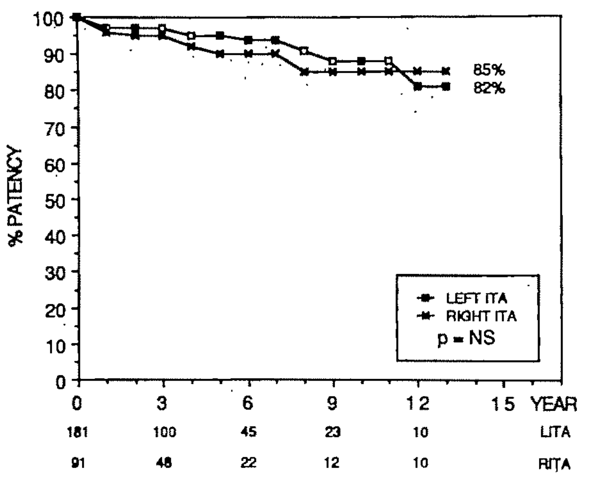

Fig 8. Actuarial patency of all left (LITA) and right internal thoracic artery (RITA) grafts. The number of grafts entering each interval is indicated beneath the abscissa.

of the ITA completely as a conduit for myocardial revascularization because of the increased time and skill required for harvest and anastomosis, combined with the concerns regarding adequacy of perfusion.

A resurgence of enthusiasm for ITA grafting occurred in 1984 when Grondin and associates [11] demonstrated that nearly 50% of saphenous vein coronary grafts became occluded by the tenth postoperative year. Internal thoracic artery grafts, on the other hand, maintained a 95% patency without signs of deterioration up to 12 years postoperatively. During this same period, Johnson and associates [12] used thallium 201 scintigraphy to demonstrate that the ITA provided excellent coronary flow even at peak myocardial demand. This confirmed the earlier clinical observations of Siegel and Loop [13] and Vogel and associates [14] that patients with multivessel coronary disease with at least one ITA graft had consistent relief of ischemia and improved exercise tolerance. Sequential arteriograms have demonstrated that ITA grafts may enlarge with time, suggesting that this arterial conduit is capable of size adaption to provide blood flow sufficient to meet the demands of the myocardium [15].

These reports answered most of the questions and criticisms regarding the benefit of an ITA conduit and led to an increased use of in situ and free ITA grafts for both single and sequential anastomoses. Improvements in operative technique, blood conservation, and myocardial protection have permitted bilateral ITA grafts to be used without the prohibitive morbidity or mortality observed earlier [16].

Perhaps the most attractive feature of the ITA is the prolonged patency and resistance to atherosclerosis. Barner and associates [17] showed experimentally that the ITA was resistant to the development of intimal hyperplasia as observed in vein grafts. Saphenous vein grafts used as arterial conduits developed fractures in the internal elastic lamina and can develop intimal hyperplasia leading to early graft closure. The ITA is particularly resistant to intimal hyperplasia because the internal elastic lamina is perfectly formed at an early age and does not fracture over time, a mechanism suggested by Sims [18] as etiologic in the development of atherosclerosis.

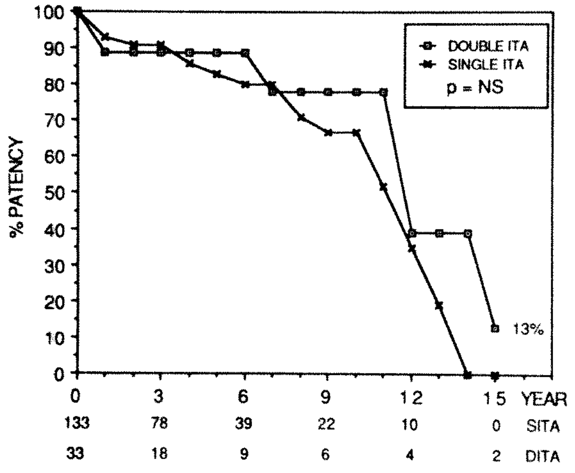

Fig 9. The actuarial patency of all saphenous vein grafts in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of grafts entering each interval is indicated beneath the abscissa.

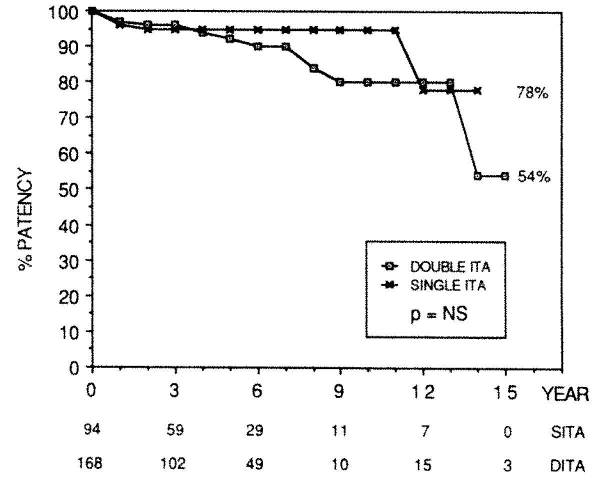

Fig 10. The actuarial patency of the internal thoracic artery in patients receiving single (SITA) or double internal thoracic artery (DITA) grafts. The number of grafts entering each interval is indicated beneath the abscissa.

Landymore and associates [19] recently demonstrated that the vasa vasorum of the ITA are confined to the adventitia and do not penetrate the media. The medial layer is nourished entirely from the lumen, which suggests that harvesting the ITA as a free graft would not subject the artery wall to ischemic injury. Recent work has raised the issue of vasoactive mediators within the wall of the ITA as protective forces against the development of atherosclerosis. Chaikouni and co-workers [20] observed that prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, is produced by endothelial cells of the human ITA at a greater level than that observed in saphenous veins. More recently, the role of endothelial relaxation factor has been investigated [21].

It has been demonstrated that one ITA graft, alone or in combination with vein grafts, gives improved survival and freedom from cardiac events when compared with vein grafts alone. In 1984, Okies and associates [22] reported a significant improvement in both actuarial and event-free survival in patients in whom the ITA was grafted to the left anterior descending coronary artery. Loop and co-workers [1] extended this observation in 1986 when they demonstrated that patients with multivessel coronary artery disease and left ventricular dysfunction enjoyed greater freedom from cardiac events when an ITA graft was placed to the left anterior descending coronary artery in lieu of a vein graft. Differences were most apparent at 10 years reflecting the persistently high ITA patency rate.

The excellent clinical results and long-term patency of single ITA grafts have inspired many surgeons to use the contralateral ITA as another arterial conduit for revascularization. Several groups reported their series of bilateral ITA grafts with excellent immediate results [16]. The question remains, however, does the use of a second ITA yield additional protective benefit when compared with use of a single ITA?

A recent report by Johnson and associates [2] compared the long-term results in patients undergoing myocardial revascularization with ITA grafts versus those with saphenous vein grafts only. When patients with bilateral ITA grafts were compared with those with single ITA grafts, no improvement in survival was noted. A similar observation was reported by Kirklin and colleagues [3], who found no significant clinical benefit when more than one ITA anastomosis was performed.

The present report strongly suggests that the addition of a second ITA graft confers a survival benefit at 15 years among hospital survivors ($p = 0.05$). Subendocardial myocardial infarction was present in five out of 11 hospital deaths that may have been related to myocardial preservation techniques then available or to inadequate ITA flow. Currently, it is possible to perform bilateral ITA grafting having an operative risk comparable with single ITA grafting or with grafting using saphenous vein only. Because we are interested in the long-term benefit, or lack thereof, of ITA grafting, it is appropriate to focus on hospital survivors as others have done [1]. Operative mortality of an earlier era is not germane to this analysis when current use of the same operation achieves a contemporary mortality.

Our 10-year survival for single (82%) and double (84%) ITA patients is similar to that reported by Cameron and associates (single ITA, 83%; double ITA, 90%) [23]. At 15 years, our survival is somewhat lower than reported by them, but the number of patients in their series followed to 15 years was smaller [23]. Galbut and co-workers [24] have reported a 12-year actuarial survival of 70% for patients receiving two ITA grafts, which is similar to our survival of 76% during this same interval.

The improvement in actuarial survival and the freedom from myocardial infarction (fatal and nonfatal) observed in our patients with two ITA grafts were more marked in the late follow-up period. This would suggest that the continued patency of both ITA grafts confers greater protection from death and myocardial infarction beyond 10 years when the attrition rate of the saphenous vein is increasing. Only by examination of late survival will these subtle differences become apparent.

The symptoms of recurrent angina pectoris were more effectively relieved in patients having two rather than one ITA graft. Lytle and associates [25] followed 71 patients with double ITA grafts for a mean of 67 months and found 69% were asymptomatic. This is similar to our experience in which 73% of the 62 patients with two ITA grafts were free from angina at 72 months. However, by 15 years, recurrent angina pectoris developed in two thirds of the double ITA group and three fourths of the single ITA group in our series. This may reflect native coronary artery disease progression, particularly in our population in which initial coronary artery stenosis less than 70% was not routinely bypassed earlier in our experience.

Angina recurrence is a "soft" end point as it is subjective. We examined the effect of two ITA grafts in patients when angina was combined with myocardial infarction and all sudden unexplained deaths (ie, all ischemic events). The presence of two ITA grafts with saphenous veins did confer an improved freedom from all ischemic events. The need for interventional therapy (percutaneous transluminal coronary angioplasty or repeat coronary bypass) in this series also was evaluated. Patients with two ITA grafts in combination with saphenous vein grafts tended to require less interventional therapy than patients with a single ITA graft and saphenous vein grafts, but this difference did not reach significance.

Since this early experience, we have changed our strategy for use of the right ITA. We currently believe that placing the right ITA in situ to the mid-right coronary artery is suboptimal, as the progression of atherosclerosis at the right coronary artery bifurcation may lead to early graft closure. If the left ITA is used for the anterior descending coronary artery, the right ITA should be grafted to the next largest coronary artery supplying the greatest area of functional myocardium. This often requires the right ITA to be used as a free graft. Several investigators have reported excellent patency using free and sequential ITA grafts [26, 27]. This has greatly expanded the usefulness of the ITA and has permitted the majority of the left ventricular muscle to be revascularized using two arterial conduits [28].

Our experience demonstrates greater longevity and increased freedom from the clinical manifestations of coronary artery disease when both ITAs are used for myocardial revascularization. This operation must be accomplished with the same low morbidity and mortality presently enjoyed for single ITA grafting. Appropriate selection is important as certain high-risk patient subgroups have been identified. This study strongly suggests a survival benefit from double ITA grafting beyond 10 years among hospital survivors. Patients whose life expectancy may be limited because of advanced age (greater than 70 years) or poor left ventricular function are generally less ideal candidates for bilateral ITA grafting. Several reports have demonstrated a higher incidence of mediastinal wound infection in diabetic patients undergoing bilateral ITA grafting. Because this complication constitutes a major cause of morbidity and mortality, we believe that elderly, obese, and diabetic patients are not candidates for bilateral ITA grafting.

As coronary artery bypass grafting enters its third decade, the use of both ITAs, supplemented with saphenous veins in selected patients, should ensure improved long-term results.

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DISCUSSION

DR GEORGE E. GREEN (New York, NY): This work contains statistical validation of the preferential advantage of using both ITAs and, as was shown, this advantage is statistically significant in terms of freedom from reoperation, freedom from angina, and improved survival.

My own experience with bilateral internal thoracic artery grafts began at about the same time as did the work reported by Fiore and associates. However, it was limited by the fact that I did not appreciate the value of the operation, and therefore, we had only 38 patients with a mean follow-up of 14 years. These 38 patients are part of a cohort of 748 patients operated on consecutively from 1970 to 1973. Five hundred thirty-two patients received mammary artery grafts, and 216 received saphenous vein grafts only.

It has been reported by many groups that patients with mammary artery grafts do better than those with saphenous veins alone. The 38 patients who had bilateral internal mammary artery grafts did best of all in the terms that Fiore and associates have described; freedom from reoperation, freedom from recurrent ischemic events, and improved survival. Because the number of patients was small, we could not use multivariate analysis. However, in general, they were similar in terms of severity of coronary disease, severity of ventricular impairment, prevalence of left main disease, and number of grafts performed.

One difference between the work of Fiore and associates and ours is that in the majority of our 38 patients, the right mammary artery was anastomosed to the anterior descending artery. In their group, it was used exclusively for the right coronary artery. I think it is all the more compelling that in both groups the selective value of using both ITAs was apparent, and I think Fiore and associates have brought us considerably closer to the wisdom of using both ITAs when performing bypass grafting.

DR CARY W. AKINS (Boston, MA): Although I enjoyed the presentation by Dr Fiore and compliment him on his excellent statistical analysis, I must point out that this study was done on hospital survivors. Actuarial survival was computed only for hospital survivors and did not account for the hospital mortality, which was 9% in the double internal mammary artery group. Their conclusion that double internal mammary artery grafting confirms improved actuarial survival is only true for hospital survivors. I would like him to comment on that statistical variation, that is, discounting hospital mortality.

DR FIORE: We all recognize Dr George Green for his pioneering efforts with single and double ITA grafting both clinically and in the laboratory beginning in 1968.

We would like to comment on the use of the right ITA. In the early era, it was placed to the right coronary artery. Currently, we believe this is suboptimal. We encourage the use of the right ITA as a free graft to bypass the posterior descending and the anterior descending coronary arteries, or a large marginal branch of the circumflex coronary artery.

Dr Akins, you raised the question of operative mortality and the fact that the results of this study focused only on hospital survivors. Five of the 11 hospital deaths were caused by subendocardial myocardial infarction. This may have been related to myocardial preservation techniques available then or to inadequate ITA flow. Currently, it is possible to perform bilateral ITA grafting with an operative risk comparable with that of single ITA grafting or grafting with saphenous vein only. Because we were interested in the long-term benefit, or lack thereof, of ITA grafting it is appropriate to focus on hospital survivors. As you know, Loop and associates [1] studied the influence of the left ITA grafted to the anterior descending coronary artery with respect to long-term survival and the occurrence of cardiac events. This study focused only on hospital survivors. We believe that operative mortality of an earlier era is not germane to this analysis when current use of the same operation should achieve a contemporary mortality.

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Risks of Bilateral Internal Mammary Artery Bypass Grafting

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Although use of one internal mammary artery (IMA) for coronary artery bypass grafting does not appear to be associated with increased risk, the results with both IMAs are less certain; the potential for a higher incidence of sternal wound infection as a result of devascularization of the sternum is a major concern. During a 42-month interval ending July 1988, 1,566 patients had coronary artery bypass grafting alone or in combination with other procedures: 633 received only vein grafts, 687 had unilateral IMA grafting, and 246 had bilateral IMA grafting. The IMA patients were younger, were more often male, had better cardiac function, and underwent fewer emergent, urgent, or combined procedures than the patients receiving vein grafts ($p < 0.05$). Thirty-day mortality was lower among the IMA patients (unilateral IMA group, 2.8%; bilateral IMA group, 3.7%; and vein graft group, 7.9%; $p = 0.001$). With the exception of sternal wound problems, occurrence rates for postoperative complications among the IMA patients did not differ significantly from or were lower ($p < 0.05$) than those among the patients with vein grafts. Sternal infections occurred with greater frequency among the bilateral IMA patients (6.9%) than among the unilateral IMA (1.9%) or vein graft (1.3%) patients ($p = 0.001$). By univariate analysis, obesity, diabetes, bilateral IMA grafting, and need for prolonged (>48 hours) mechanical ventilation were associated with a significantly higher incidence of sternal infection ($p < 0.05$). Multivariate logistic regression analysis identified use of bilateral IMA grafts ($p = 0.0001$), obesity ($p = 0.0014$), and prolonged mechanical ventilation ($p = 0.0018$) as significant risk factors for the development of sternal infection. We conclude that bilateral IMA grafting is an important predictor of sternal infection. It should be used selectively in obese or diabetic patients and in patients who are likely to require prolonged mechanical ventilation postoperatively.

(Ann Thorac Surg 1990;49:210–9)

The internal mammary artery (IMA) is currently the conduit of choice for coronary artery bypass grafting (CABG). Although the use of one IMA does not appear to be associated with increased operative risk, the results with both IMAs are less certain. A major concern when both IMAs are used is the potential for a higher incidence of sternal wound complications, presumably as a result of devascularization of the sternum [1–5]. We have reviewed our entire experience with CABG during a recent 3½-year interval to determine if use of bilateral IMA grafts is associated with increased risk, and to identify those variables that are predictive of an increased risk of sternal wound infection.

Material and Methods

Patients

Between January 1985 and July 1988, 1,566 patients underwent CABG alone or in combination with other procedures (resection of ventricular aneurysm or infarct, repair of rupture of the ventricular septum, valve replacement or repair, replacement of the ascending aorta and arch, and carotid endarterectomy). Vein grafts (VGs) only were used in 633 patients, one IMA graft was used in 687 patients, and bilateral IMA grafts were used in 246 patients. Vein grafts were also used in 864 (93%) of the 933 patients receiving IMA grafts.

Clinical Presentation

The preoperative characteristics of the patients in the three groups are shown in Table 1. Diabetes was considered present in patients who were receiving insulin or oral hypoglycemic agents or who had been placed on carbohydrate- and calorie-restricted diets by a physician. Hypertension was defined as a resting blood pressure of 140/90 mm Hg or higher; it was also considered present in patients who were receiving antihypertensive medication. To evaluate the effect of obesity, the body mass or the Quetelet index (body weight in kilograms divided by the square of the height in meters) was used [4, 5]. This expression of weight in relation to height has a better correlation to body fat than other height-weight relationships. At 30 kg/m^2 or more, obesity and overweight are essentially synonymous. Above this level, mortality for coronary heart disease for both men and women increases [5]. Chronic obstructive pulmonary disease was considered present in patients with characteristic findings on roentgenograms (pulmonary hyperinflation, flattened diaphragms, and oligemia of the peripheral lung fields) or on diagnostic pulmonary function tests. Angina pectoris

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was defined according to the Canadian Cardiovascular Society classification [6].

Catheterization Data

The extent of coronary artery disease is shown in Table 2. Stenoses greater than 50% to 60% of the luminal diameter were considered hemodynamically significant. Patients were classified as having one-vessel, two-vessel, three-vessel, or left main coronary artery disease. Major stenoses in the large diagonal or obtuse marginal branches were considered lesions of the anterior descending or circumflex coronary arteries, respectively. Ventriculography was performed in the right anterior oblique projection. Five segments (anterobasal, anterolateral, apical, diaphragmatic, and posterobasal) were analyzed and assigned a numerical score (1 = normal; 2 = moderate hypokinesis; 3 = severe hypokinesis; 4 = akinesia; 5 = dyskinesia; and 6 = aneurysm) according to the classification of the Coronary Artery Surgery Study [7]. Ventriculograms suitable for analysis were available for 1,381 (88%) of the 1,566 patients.

Perioperative Protocol

All operations were performed by or under the direct supervision of two surgeons (N.T.K., W.G.M.) using a standardized technique. Cardiopulmonary bypass with moderate core hypothermia (24° to 28°C) and hemodilution was used in all patients. The IMAs were mobilized with a pedicle from the bifurcation into the superficial epigastric and musculophrenic branches to their origin. Low-current electrocoagulation was used to mobilize the pedicle, and clips were applied to the larger intercostal branches.

Table 1. Preoperative Characteristics of the Patient Groups[a]

Variable	Vein Grafts Only (n = 633)	Unilateral IMA Graft (n = 687)	Bilateral IMA Grafts (n = 246)
Mean age (yr)	69.8	61.6	55.5
Age ≥ 65 yr	479 (76)	289 (42)	33 (13)
Male sex	372 (59)	501 (73)	207 (84)
Diabetes	167 (26)	174 (25)	56 (23)
Hypertension	386 (61)	415 (60)	134 (55)
Obesity index ≥ 30 kg/m²	90 (14)	148 (22)	54 (22)
Chronic obstructive pulmonary disease	41 (6.5)	30 (4.4)	8 (3.3)
History of smoking	357 (56)	450 (66)	180 (73)
Previous myocardial infarction	433 (68)	369 (54)	139 (57)
History of congestive failure	266 (42)	129 (19)	33 (13)
CCS class II–IV	573 (91)	643 (94)	229 (93)
Previous cardiac operation	65 (10)	71 (10)	18 (7.3)
More than two days from admission to operation	350 (55)	329 (48)	100 (41)

[a] Numbers in parentheses are percentages.

CCS = Canadian Cardiovascular Society; IMA = internal mammary artery.

Table 2. Cardiac Catheterization Data[a]

Variable	Vein Grafts Only (n = 633)	Unilateral IMA Grafts (n = 687)	Bilateral IMA Grafts (n = 246)
Extent of disease			
One vessel	50 (7.9)	45 (6.6)	0 . . .
Two vessels	113 (17.9)	147 (21.4)	37 (15.0)
Three vessels	353 (55.8)	412 (60.0)	169 (68.7)
Left main coronary artery	117 (18.5)	83 (12.1)	40 (16.3)
Left ventricular wall motion score (CASS)[b]			
5	115 (21.0)	194 (32.1)	68 (29.6)
6–10	156 (28.5)	204 (33.8)	83 (36.1)
11–15	158 (28.9)	149 (24.7)	65 (28.3)
16–30	118 (21.6)	57 (9.4)	14 (6.1)
Mean score	11.1 ± 4.7	9.2 ± 4.1	9.1 ± 3.8

[a] Numbers in parentheses are percentages. [b] Data were not available for all patients.

CASS = Coronary Artery Surgery Study; IMA = internal mammary artery.

The distal anastomoses were performed first after administration of a cold crystalloid oxygenated cardioplegic solution (septal temperature, 10° to 12°C) with additional infusions every 20 to 30 minutes. Anastomoses of the VGs or, on occasion, the IMA grafts to the aorta were performed after release of the aortic clamp while the patients were rewarmed to 34°C (rectal or bladder temperature). The sternal edges were reapproximated with five to seven stainless steel wires, which were tightened by manual twisting. The rectus fascia was closed with interrupted braided Dacron sutures. The subcutaneous tissues were closed with one or two layers of continuous absorbable suture. Intravenous antibiotics were administered preoperatively and were continued for 48 hours postoperatively. The number of patients requiring emergent or urgent operation (within 24 hours of cardiac catheterization), the durations of cardiopulmonary bypass and aortic occlusion, the mean number of arteries grafted, and the number of patients undergoing isolated CABG for the three groups are shown in Table 3.

Electrocardiograms were obtained on the first and sixth postoperative days. Serum creatine kinase and lactate dehydrogenase (LDH) levels (total and fractionated) were measured 1, 12, and 24 hours postoperatively. The presence of a new Q wave or a ratio of LDH_1 to LDH_2 of 1 or greater was considered indicative of perioperative myocardial infarction. Postoperative low cardiac output was considered present when inotropic support (infusion of dopamine hydrochloride or dobutamine hydrochloride at 5 μg/kg/min or more) was required for more than 24 hours. Stroke was defined as any transient or permanent focal neurological deficit. Sternal infection was considered present in patients in whom sternal instability developed

Table 3. Operative Data[a]

Variable	Vein Grafts Only (n = 633)	Unilateral IMA Graft (n = 687)	Bilateral IMA Grafts (n = 246)
Emergent or urgent operation	58 (9.2)	4 (0.6)	1 (0.4)
Duration of cardiopulmonary bypass (min)	124 ± 45	113 ± 32	124 ± 28
Duration of aortic occlusion (min)	69 ± 29	69 ± 23	78 ± 19
Mean no. of arteries grafted	3.5 ± 1.3	3.8 ± 1.3	4.0 ± 1.0
Isolated CABG	413 (65)	624 (91)	243 (99)

[a] Numbers in parentheses are percentages.

CABG = coronary artery bypass grafting; IMA = internal mammary artery.

in association with positive wound cultures and in whom a second surgical procedure (incision and drainage, removal of the sternal wires with debridement, and secondary closure) was required. Superficial wound infections responding to conservative treatment, sterile wound dehiscences, and wounds demonstrating delayed healing were classified separately.

The patients were also stratified according to surgeon, two different antibiotic regimens (one employed before and one after July 1, 1987), presence or absence of a high-laminar-flow operating room (which became available on June 1, 1987), and duration of hospitalization before CABG.

Data Management and Statistical Analysis

All data were compiled and stored in a computerized data bank using an IBM 3270 system and were analyzed with SAS (SAS Institute Inc, Cary, NC) on the Washington University Division of Biostatistics computer system. Continuous data were recorded as the mean ± the standard deviation.

Univariate analysis with χ^2 testing for proportions or analysis of variance for means was used to compare the characteristics of the three groups of patients. If test results were significant ($p < 0.05$), then pairwise comparisons were performed to determine if differences occurred between all pairings of surgical methods [8]. Univariate analysis was also used to assess the effect of 21 categorical variables on the development of sternal infection (Appendix 1). These variables were selected in part from a review of publications relating to sternal wound infection in which a number of variables were evaluated for possible association with this complication [9–13]. Multivariate logistic regression was used to select the independent predictors of sternal infection.

These analyses were performed using PROC CATMOD (SAS) to obtain maximum likelihood estimates. A p value of less than 0.05 was considered significant. Conditional odds ratios for the significant variables and predicted proportions of patients infected for all possible categories were obtained from the logistic regression [14].

Results

Compared with the VG patients, the unilateral and bilateral IMA patients were younger, were more often male, had a lower incidence of previous myocardial infarction, congestive heart failure, and severely depressed left ventricular function (wall motion score, 16 to 30), and had a higher prevalence of obesity and smoking (see Tables 1, 2). The IMA patients underwent fewer emergent, urgent, or combined operative procedures and had a shorter average period of hospitalization before operation than the VG patients (see Tables 1, 3). The number of arteries grafted among the IMA patients was higher (see Table 3). All of these differences were significant ($p < 0.05$).

The bilateral IMA patients were younger than the unilateral IMA patients, were more often male, and had a higher prevalence of smoking ($p < 0.05$) (see Table 1). No other significant differences in baseline or operative characteristics were observed between these two groups.

Mortality

Thirty-day mortality was lower among the IMA patients than among the VG patients (unilateral IMA group, 2.8%; bilateral IMA group, 3.7%; and VG group, 7.9%) (Table 4). The differences between the unilateral IMA and VG groups and between the bilateral IMA and VG groups were significant ($p = 0.001$). Sixty-two of the 78 postoperative deaths were of cardiac origin. Only 1 of the postoperative deaths was directly attributable to the development of a sternal wound infection.

Table 4. Mortality and Morbidity[a]

Variable	Vein Grafts Only (n = 633)	Unilateral IMA Graft (n = 687)	Bilateral IMA Grafts (n = 246)
30-day mortality	50 (7.9)	19 (2.8)	9 (3.7)
Perioperative myocardial infarction	5 (0.8)	14 (2.0)	5 (2.0)
Low cardiac output	41 (6.5)	30 (4.4)	8 (3.3)
Intraaortic balloon pump	77 (12.2)	22 (3.2)	11 (4.5)
Reoperation for bleeding	23 (3.6)	32 (4.7)	13 (5.3)
Transfusion requirements			
No blood products	99 (15.6)	213 (31.0)	103 (41.9)
Mean no. of units/ patient	3.9	2.5	2.1
Stroke	29 (4.6)	14 (2.0)	2 (0.8)
Mechanical ventilation >48 h	90 (14.2)	36 (5.2)	21 (8.5)
Pneumonia	38 (6.0)	17 (2.5)	11 (4.5)
Sternal infection	8 (1.3)	13 (1.9)	17 (6.9)
Superficial chest wound infection, sterile dehiscence, or delayed healing	14 (2.2)	20 (2.9)	25 (10.2)

[a] Numbers in parentheses are percentages.

IMA = internal mammary artery.

Table 5. Predictors of Sternal Infection by Multivariate Analysis With Logistic Regression

Variable	Degrees of Freedom	χ^2	p Value	Odds Ratio
Bypass procedure	2	19.99	0.0001	1.64 1 IMA vs veins 5.95 2 IMAs vs veins 3.63 2 IMAs vs 1 IMA
Obesity index ≥30 kg/m^2	1	10.19	0.0014	3.00
Mechanical ventilation >48 h	1	9.76	0.0018	3.64

IMA = internal mammary artery.

Morbidity

No significant differences in the incidence of perioperative myocardial infarction, low cardiac output, and reoperation for bleeding were observed among the three groups (see Table 4). The need for postoperative intraaortic balloon pumping, transfusion of blood products, and prolonged mechanical ventilation was significantly greater among the VG patients than either the unilateral or bilateral IMA patients ($p < 0.01$). The incidence of stroke was higher in the VG group than the bilateral IMA group ($p < 0.01$), and the incidence of postoperative pneumonia was higher among the VG patients than among the unilateral IMA patients ($p = 0.05$). None of the other differences between groups for these events were significant.

Sternal infections occurred with greater frequency among the bilateral IMA patients (6.9%) than among the unilateral IMA (1.9%) or VG (1.3%) patients (Fig 1; see Table 4). The differences between the bilateral IMA and unilateral IMA groups and between the bilateral IMA and VG groups were significant ($p < 0.001$). Among the 413 VG patients having isolated CABG and the 220 VG patients having combined procedures, the incidence of sternal infection was 1.0% (4 patients) and 1.8% (4 patients), respectively ($p = 0.4$). The prevalence of sternal infection was significantly higher in diabetic patients overall (3.8% versus 2.0%; $p = 0.04$) (Appendix 2) and among diabetic patients receiving IMA grafts (bilateral IMA group, 12.5% versus 5.3% [$p = 0.06$]; unilateral IMA group, 4.0% versus 1.2% [$p = 0.02$]; and VG group, 0.6% versus 1.5% [$p = 0.4$]).

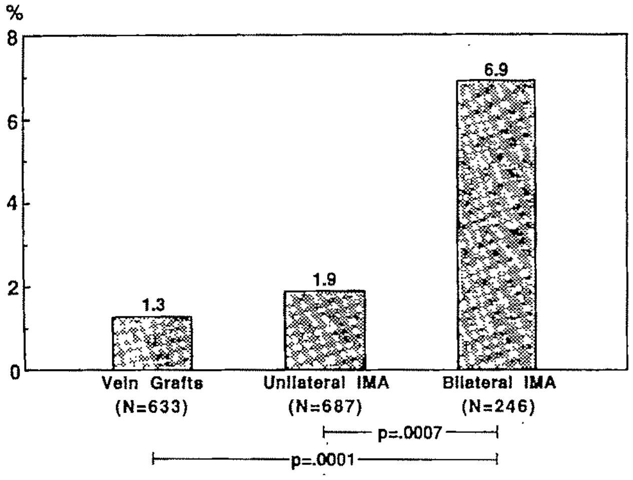


Fig 1. Incidence of sternal infection according to type of bypass graft. (IMA = internal mammary artery.)

By univariate analysis, obesity index of 30 kg/m^2 or greater, diabetes, bilateral IMA grafting, and prolonged mechanical ventilation were associated with a significantly higher incidence of sternal infection ($p < 0.05$). The increased incidence of infection in patients requiring reoperation for bleeding approached significance ($p = 0.07$) (see Appendix 2). In the multivariate analysis, bilateral IMA grafting, obesity index of 30 kg/m^2 or greater, and prolonged mechanical ventilation were significant independent predictors associated with the development of sternal infection (Table 5).

Logit scores and the predicted proportions of patients infected were computed for the 12 possible categories using the three significant variables (Fig 2; Appendix 3). The group with the lowest predicted risk of infection (0.7%) received VGs only, had an obesity index of less than 30 kg/m^2, and did not require prolonged ventilation. The group with the highest predicted risk of infection (32.3%) received bilateral IMA grafts, had an obesity index of 30 kg/m^2 or higher, and required prolonged mechanical ventilation.

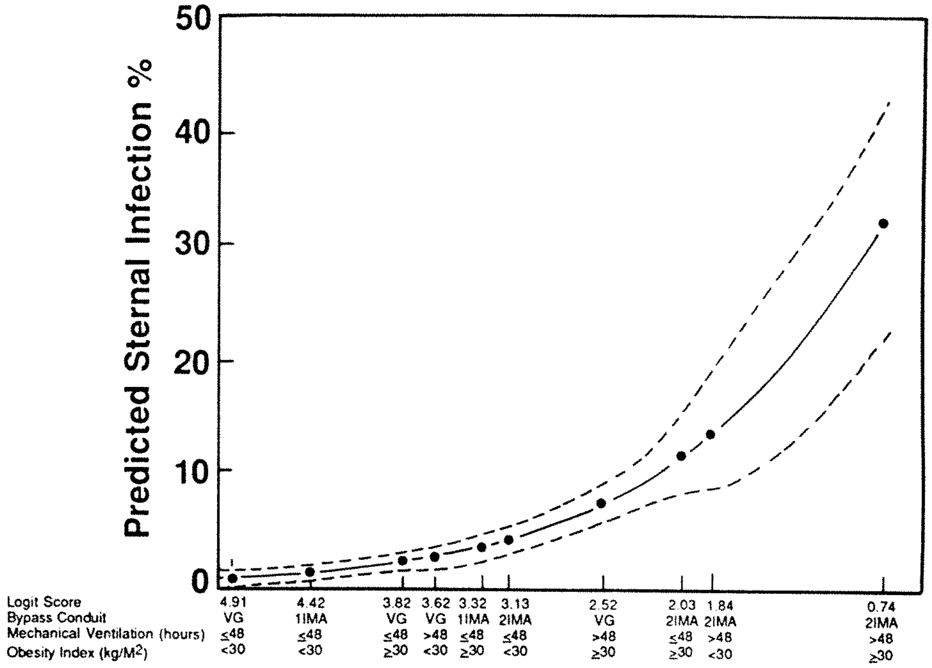
The incidence of superficial chest wound infection, sterile dehiscence, and delayed healing in the aggregate was also significantly higher among the bilateral IMA patients than among the VG and unilateral IMA patients ($p < 0.05$) (see Table 4).

Comment

Because of its superior long-term patency and the associated beneficial effect on long-term survival, reoperation-free survival, and need for subsequent hospitalization for cardiac-related events compared with VGs, the IMA is currently the conduit of choice for CABG [15–17]. In studies [15–17] that have evaluated the relative effectiveness of IMAs and VGs, the majority of patients received only one IMA graft.

It has not been conclusively demonstrated that use of both IMAs provides additional benefit over the use of one IMA. In general, bilateral IMA grafting has been employed selectively [1–3, 18–22]. In studies [2, 3, 20, 21] comparing patients who underwent bilateral IMA grafting with those who received only VGs or in whom unilateral IMA grafting was used, hospital mortality rates were not significantly greater among the bilateral IMA groups. A significantly higher incidence of perioperative myocardial infarction among the bilateral IMA patients compared with patients who received only VGs was reported by

Fig 2. Logit curve for the three independent predictors of sternal infection (bypass procedure, obesity index, and prolonged mechanical ventilation). Broken lines *represent the standard error. (*1IMA *= one internal mammary artery;* 2IMA *= both internal mammary arteries;* VG *= vein grafts.)*



Buxton and co-workers [21]. Cosgrove and associates [3] documented a significantly greater incidence of blood transfusion among patients with bilateral IMA grafts compared with patients with unilateral IMA grafts and those with VGs only.

In the present study, use of bilateral IMA grafts was not associated with increased 30-day mortality compared with single IMA or venous grafting. Early mortality was similar for the unilateral and bilateral IMA patients and was significantly lower for these two groups than for the VG patients (see Table 4). This lower mortality rate was related in a major way to the criteria used to select patients for IMA grafting. The IMA patients were younger, had less preoperative impairment of left ventricular function, and underwent fewer combined, emergent, or urgent procedures. Similar differences in mortality, also related to differing baseline characteristics and selection criteria, have been reported by Jones [2], Cosgrove [3], and their colleagues.

With the exceptions of sternal infection and other chest wound problems, none of the other postoperative complications evaluated occurred with greater frequency among the patients receiving unilateral or bilateral IMA grafts than among the VG patients. The prevalence of sternal wound complications was significantly higher among the bilateral IMA patients than the other two groups. In the multivariate analysis, choice of conduit was the most significant predictor for the development of sternal infection.

We evaluated a number of variables that have been reported in previous studies [9–13] to be associated with an increased risk of sternal wound infection. Despite the greater prevalence in the VG group of several variables (female sex [10], depressed left ventricular function [13], combined procedures [12], postoperative low cardiac output [12], and prolonged ventilatory support [10, 13]) reported to be associated with a higher incidence of sternal wound infection, the overall incidence of this complication was 1.3%, lower than that for either the unilateral or bilateral IMA group, but comparable with that reported in other series [11, 13].

The reported incidence of sternal wound infection in patients receiving bilateral IMA grafts has ranged from 1.6% to 8.5% [1, 9, 18, 19, 21]. In the studies in which comparisons of sternal infection rates were made with patients receiving unilateral IMA grafts or VGs, a higher sternal infection rate was uniformly observed among the bilateral IMA patients [3, 9, 21, 23]. Comparing a group of bilateral IMA patients with identical numbers of patients who were matched for factors associated with increased operative risk and who received either unilateral IMA grafts or VGs, Cosgrove and associates [3] observed a significantly higher incidence of sternal wound complications among the bilateral IMA patients. In a multivariate analysis that examined four variables (age, sex, diabetic state, and number of IMA grafts) for their association with sternal wound complications, diabetes and advanced age emerged as significant variables.

In our study, diabetes was a significant predictor for the development of sternal infection in the univariate but not the multivariate analysis. The strong association between obesity, a significant predictor in the multivariate analysis, and diabetes in our patients may have weakened the predictive value of diabetes. The higher prevalence of sternal infection in all three groups in our series compared with similar groups in the series of Cosgrove [3], Buxton [21], and their co-workers may be related to a greater than twofold higher prevalence of diabetes among the patients in our study and possibly to other differences in patient characteristics and patient management. Other variables, not examined in our study or the study of Cosgrove and colleagues [3], might also have independent predictive value for the development of sternal infection.

Devascularization of the sternum as a result of mobilization of one or both IMAs has been postulated as a mechanism for the development of sternal wound infection after myocardial revascularization. The elegant anatomical studies of the blood supply of the sternum in humans by Arnold [24] and the studies of sternal blood flow after sternotomy and mobilization of the IMAs in baboons by Seyfer and associates [25] indicate that the IMAs are the principal source of blood supply to the sternum, and that mobilization of the IMA significantly reduces blood flow to that half of the sternum. These studies and the clinical studies comparing the prevalence of sternal wound infection in bilateral IMA, unilateral IMA, and VG patients strongly suggest that devascularization of the sternum is an important determinant of the development of sternal wound complications.

In our study, the presence of other risk factors (obesity and prolonged mechanical ventilation) also increased the risk for development of sternal infection (see Fig 1; Appendix 3). Increasing weight and obesity have been shown to be significant independent predictors for the development of sternal infection [10, 26]. Prolonged mechanical ventilation has also been shown to be a significant predictor by univariate and multivariate analyses [10, 13].

In the present study, use of bilateral IMA grafts was the strongest predictor for the development of sternal infection among patients having coronary artery bypass procedures (see Table 5). Until the superiority of bilateral over unilateral IMA grafting is clearly demonstrated, we believe that bilateral IMA grafting should continue to be employed selectively. Our analyses suggest that patients with bilateral IMA grafts who are obese and who require prolonged ventilatory support are at increased risk for the development of sternal infection. The estimated risk exceeds 10% in these subgroups (see Appendix 3). Patients who receive only VGs or unilateral IMA grafts are also at increased risk (>7%) if obesity is present and prolonged mechanical ventilation is required. Bilateral IMA grafting should also be used selectively in diabetic patients. Although the mortality for sternal wound infection was not excessive in our study, the increased morbidity, including the need for additional surgical procedures and prolonged hospitalization, does not appear to justify the use of bilateral IMA grafts in high-risk patients unless other conduits are not available.

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Appendix 1. Variables Tested for Association With Sternal Infection

Preoperative Clinical Variables

- Age
  - <65 yr
  - ≥65 yr
- Sex
- Diabetes
- Chronic obstructive pulmonary disease
- Obesity index
  - <30 kg/m^2
  - ≥30 kg/m^2
- Previous cardiac operation
- Left main coronary artery disease
- Left ventricular wall motion score
  - 5
  - 6–10
  - 11–15
  - 16–30
- Length of hospitalization before CABG
  - ≤2 days
  - >2 days

Operation-Related Variables

- Surgeon
- Emergent or urgent operations
- Type of operation
  - Isolated CABG
  - Combined procedure
- Bypass procedure
  - Vein grafts only
  - Unilateral IMA grafting
  - Bilateral IMA grafting
- Duration of cardiopulmonary bypass
  - <113 min
  - ≥113 min
- Laminar-flow operating room

Postoperative Variables

- Reoperation for bleeding
- Blood transfusion
- Low cardiac output
- Mechanical ventilation
  - ≤48 h
  - >48 h
- Pneumonia
- Antibiotic regimen

Appendix 2. Predictors of Sternal Infection by Univariate Analysis

Variable	No. of Sternal Infections/ Total Patients	%	*p* Value
Overall	38/1,566	2.4	
Age			
<65 yr	24/766	3.1	0.08
≥65 yr	14/800	1.8	
Sex			
Male	24/1079	2.2	0.44
Female	14/487	2.9	
Diabetes			
No	23/1,170	2.0	0.04
Yes	15/396	3.8	
Chronic obstructive pulmonary disease			
No	34/1,487	2.3	0.12
Yes	4/79	5.1	
Obesity index			
<30 kg/m^2	22/1,274	1.7	0.001
≥30 kg/m^2	16/292	5.5	
Previous cardiac operation			
No	36/1,413	2.5	0.34
Yes	2/153	1.3	
Left main coronary disease			
No	30/1,326	2.3	0.32
Yes	8/240	3.3	
Left ventricular wall motion score			
5	6/377	1.6	0.47
6–10	13/443	2.9	
11–15	7/372	1.9	
16–30	6/189	3.2	
Preoperative hospital stay			
≤2 days	12/611	2.0	0.34
>2 days	26/955	2.7	
Surgeon			
A	23/990	2.3	0.66
B	15/558	2.7	
Emergent/urgent operation			
No	32/1,255	2.5	0.52
Yes	6/311	1.9	
Type of operation			
Isolated CABG	32/1,278	2.5	0.68
Combined procedure	6/288	2.1	
Bypass procedure			
Vein grafts only	8/633	1.3	<0.0001
Unilateral IMA	13/687	1.9	
Bilateral IMA	17/246	6.9	
Duration of cardiopulmonary bypass			
<113 min	15/769	2.0	0.23
≥113 min	23/797	2.9	
Laminar-flow operating room			
No	5/236	2.1	0.74
Yes	33/1,330	2.5	
Reoperation for bleeding			
No	34/1,496	2.3	0.07
Yes	4/70	5.7	
Blood transfusion			
No	10/410	2.4	0.99
Yes	28/1,156	2.4	

Appendix 2. Continued

Variable	No. of Sternal Infections/ Total Patients	%	*p* Value
Low cardiac output			
No	33/1,393	2.4	0.67
Yes	5/173	2.9	
Mechanical ventilation			
≤48 h	29/1,420	2.0	0.002
>48 h	9/146	6.2	
Pneumonia			
No	35/1,500	2.3	0.25
Yes	3/66	4.5	
Antibiotic regimen			
A	33/1,330	2.5	0.74
B	5/236	2.1	

CABG = coronary artery bypass grafting; IMA = internal mammary artery.

Appendix 3. Logit Scores and Predicted Sternal Infection Rates for Patient Groups Using the Three Independently Predictive Variables

Bypass Conduit	Mechanical Ventilation (h)	Obesity Index (kg/m^2)	Predicted		
			Logit Score	Proportion Infected	Standard Error
Veins	≤48	<30	4.91	0.007	0.003
1 IMA	≤48	<30	4.42	0.012	0.004
Veins	≤48	≥30	3.82	0.022	0.010
Veins	>48	<30	3.62	0.026	0.012
1 IMA	≤48	≥30	3.32	0.035	0.012
2 IMAs	≤48	<30	3.13	0.042	0.012
1 IMA	>48	<30	3.13	0.042	0.019
Veins	>48	≥30	2.52	0.074	0.035
2 IMAs	≤48	≥30	2.03	0.116	0.035
1 IMA	>48	≥30	2.03	0.116	0.050
2 IMAs	>48	<30	1.84	0.137	0.053
2 IMAs	>48	≥30	0.74	0.323	0.101

IMA = internal mammary artery.

DISCUSSION

DR ALEXANDER S. GEHA (Cleveland, OH): Our own experience with the double internal mammary artery is pretty much in line with that of Kouchoukos and associates, as far as the early risks and complications. Although our series has a smaller number of patients with bilateral IMA grafts, the use of the double IMA appears to add to the risks of sternal complications in these patients.

I want to mention some of the results that we have encountered over the long term with the use of the double IMA, predominantly grafting the left IMA to the left anterior descending coronary artery and the right IMA to either the diagonal or circumflex coronary artery, and oftentimes passing the right IMA in the transverse sinus behind the pulmonary artery and the aorta. In the early days of our experience with coronary bypass grafting between 1973 and 1978, we had considerable enthusiasm for the use of the left IMA and enthusiasm for using both IMAs for crossed double IMA grafting in select patients who were predominantly male and younger, somewhat similar to those in the St. Louis University series of Dr Fiore and associates [1]. We therefore took advantage of a long-term follow-up, and in 1987 reviewed the results over 10 years in these patients and tried to match them with a series of patients who had similar demographic and clinical characteristics, and who had only vein grafts instead of double IMA grafts placed into similar coronary vessels during that same historical period.

Over 10 years of follow-up, the linearized incidence of events shows considerably fewer cardiac-related deaths, reoperations, recurrent angina, and myocardial infarctions in the group who received the double IMA versus veins only. Mind you, we did not compare the double mammary group with another having a single left IMA graft to the left anterior descending coronary artery and a vein graft to another vessel. The actuarial curves also show significantly greater freedom from cardiac death, from myocardial infarction, from recurrent angina, and from reoperation for the group who received those crossed double IMA grafts instead of the group who received veins only.

Dr Kouchoukos has very appropriately pointed out that his group of patients with double IMA grafts was younger, had a male predominance and a lower incidence of myocardial infarction, congestive heart failure, and decreased ejection fraction, and had fewer emergent operations and fewer urgent operations or combined operations than his group with vein grafts only. I think this is the key because the selection of patients who receive double IMA grafts at this time is, as he pointed out, very crucial. We still are debating even the early risks of the operation. We heard in the report by Loop and associates [2] that the use of the double IMA graft was not in itself, without the presence of diabetes, a predictor of sternal wound complications. The paper by Kouchoukos and associates suggests a different conclusion.

The long-term results also are not all in, and therefore I want to sound a note of caution that the use of the right IMA, especially as a natural pedicle to graft very distal vessels, should be done with utmost care in select patients by those who have experience with it. Its indiscriminate use, I am afraid, may lead sometimes to disastrous operative results if one overextends its use in an attempt to achieve a long-term benefit.

DR JOHN E. ANDERSON (Boston, MA): I would like to present the experience of a single surgeon extending over 24 months involving 133 patients. This is a smaller series and represents the experience of a surgeon not receiving training in mammary artery grafting during his residency training program.

Of the total patients, 238 received coronary revascularization; 56% of these patients received bilateral internal mammary artery grafts. The 238 patients receiving coronary revascularization represents approximately half of this surgeon's surgical experience, the other half consisting of isolated valve operations and congenital cardiac operations. The surgical policy has been to find a reason not to do bilateral mammary revascularization instead of finding a reason to do it.

In this series of 133 patients, 80% were male, 20% had an ejection fraction ranging from 20% to 40%, and 26% of the series were diabetics. The age range indicates that the majority of patients were in either their sixth or seventh decade of life.

At the time of operation, the majority of patients (61%) received one mammary artery graft to one coronary artery. As experience has progressed with this technique, there has been a trend toward bilateral sequential revascularization, which is 28% of this series. When extra mammary artery is available, sutured Y grafts are established to increase the number of coronary arteries revascularized with mammary conduit.

Operative strategy for mammary revascularization included use of a 2 to 6-cm patch arterioplasty of mammary artery in 27% of this series. This was primarily for midsegment stenosis in the left anterior descending coronary artery. A free mammary artery graft was used in 15% of this series and endarterectomy of the revascularized coronary artery was required in 11% of this series.

No operative or hospital mortality has been incurred in this series. Reoperation for bleeding was required in 4 patients (3.8%) early in this experience. Perioperative neurological insult occurred in 3 patients, all of whom recovered. Two patients (1.5%) incurred a perioperative myocardial infarction.

With respect to sternal wound complications, the results are similar to those of the series of Kouchoukos and associates. Early infection developed in 4.5% of the patients. Dehiscence without infection developed in 1 patient, late sternal osteomyelitis developed in 1 patient 3 months after operation, and a late dehischence of the sternotomy incision developed in 1 patient more than 6 months after operation. In evaluating this small series, factors that were found not to be related to infection or sternal complication rate were (1) body mass to height ratio (I believe we will have to reevaluate our data in a more sophisticated way as Kouchoukos and associates have done); (2) length of postoperative ventilation (107 of 133 patients or 80% were extubated from ventilatory support on the first postoperative day; therefore our numbers were too small to show a relation to wound infection risk); (3) cross-clamp time; (4) perfusion time; (5) operating time; and (6) reoperation for bleeding. The two factors in this series that were related to the risk of wound infection were diabetes and age greater than 70 years.

Dr Kouchoukos, is what is your attitude currently toward revascularization in insulin-dependent diabetics who are not obese and elderly? Also, could the benefit of bilateral IMA revascularization over single IMA revascularization be more quickly shown in patients operated on in their seventh decade of life?

DR ALFRED T. CULLIFORD (New York, NY): During this meeting six papers have addressed various ramifications of IMA grafting. This unprecedented amount of attention has focused on operative mortality, recurrent angina, survival, freedom from infarction, old age, and the varying results obtained with bilateral IMA implants. After 2½ decades of clinical experience and considerable discussion, the IMA remains the conduit of choice for many of us here.

Dr Kouchoukos and associates have observed an increase in infection rate when bilateral mammary arteries are employed and identified several risk factors responsible for this increase.

This association has been studied in detail at New York University. In 1976 we noted an infection rate of 8.5% when bilateral IMA grafts were employed and were both pleased and relieved to note that it decreased to just under 4% when 135 recent patients with bilateral implants were reviewed.

An important study was conducted by Dr Arnold in 1972 concerning sternal blood supply. The blood supply to the sternum rises from a periostial arcade arising from the internal mammary artery. This was visualized by Dr Arnold in a laboratory preparation after injecting the mammary vessel; rich arborizing branches could be seen arising from both mammary arteries. When, however, another laboratory preparation was made in which both mammary arteries were mobilized, these arcades filled very poorly, suggesting the possibility that relative sternal ischemia may occur.

With this in mind it is easy to understand why factors such as diabetes, obesity, low cardiac output, and prolonged ventilatory support were identified by Kouchoukos and associates as important risk factors. The decision to employ both IMAs then becomes a formulation of a risk/benefit ratio. If too many risk factors are present, the benefit declines and the price for this decision is paid for by the patient in terms of morbidity and mortality.

With this in mind I have two questions. In which patients would you continue to use bilateral IMA grafts? Would age alone exclude someone or would the presence of one, two, or three risk factors exclude someone? Finally, in the medical-legal age, should we emphasize these increased risks to our patients as part of an informed consent?

DR NOEL L. MILLS (New Orleans, LA): In analyzing these reports, it becomes apparent that there is a real difference in the statistics between those of the group in Miami [3] and those by Dr Kouchoukos' group. When one looks at these reports one finds that the group from Miami took the IMA down skeletonized as a single vessel as opposed to a pedicle, which obviously is more damaging to tissues and collateral circulation. It may be that in diabetics—and both of those papers had comparable groups of diabetics, 20% to 25%—we should at least take one IMA down as a skeletonized vessel.

I would like to also point out that it behooves us to know the crest factor of our individual electrosurgical units. Ten to 11 is optimal to avoid tissue destruction.

DR RICHARD K. HUGHES (Los Angeles, CA): Just in case everybody is going to go home and do bilateral IMA grafts, it is my understanding that, at least in some institutions, there is concern about bringing the right IMA over to the front of the left side of the heart because of the risk of possible injury at reoperation. In younger patients, bringing the right IMA across in front of the heart may subject a patient to risk if reoperation is necessary. I would like to have Dr Kouchoukos comment on this point.

DR KOUCHOUKOS: Dr Geha has presented important information on the long-term results of bilateral IMA grafting. As I recall, that study excluded hospital mortality from the actuarial analysis of survival. The results must therefore be interpreted with this in mind and appear similar to those presented earlier by Dr Fiore [1].

I appreciate Dr Anderson's comments. His results are similar to those that we presented. As a result of our analyses, we have adopted a more conservative view toward bilateral IMA grafting. We currently do not perform the procedure in obese, diabetic patients or in patients over the age of 70 years unless other suitable conduits are unavailable. We will continue this policy until data become available that demonstrate a greater benefit of bilateral over unilateral IMA grafting. We believe that bilateral IMA grafting may have a beneficial effect in young patients, especially those with elevated cholesterol and triglyceride levels, and continue to use it in this subset, even in the presence of diabetes and obesity, recognizing that there may be an increased incidence of sternal wound complications. It is important, as Dr Culliford pointed out, that this increased risk be explained to the patient before operation.

Dr Mills, I do not have any information about the possible beneficial effect of skeletonization of the IMA. Dr Culliford showed us some of the results of the elegant study of Dr Arnold that indicate that interruption of the major branches of the IMA results in devascularization of the sternum and appears to be an important factor for the development of sternal wound complications, particularly if other risk factors for infection are present.

Dr Hughes, we use the right IMA as a pedicle graft in about half the cases of bilateral IMA grafting, and almost always anastomose it to the anterior descending coronary artery. In the remaining cases it is used as a free graft to the anterior descending or circumflex systems. We rarely attach it to the right coronary artery. We too are concerned about the risk of injury to the artery at reoperation, but to date this has not occurred.

A major point we wish to make is that if bilateral IMA grafting is applied to patients with other risk factors for infection, the rate of sternal infection will be substantially increased. Because of the increased mortality, morbidity, and cost associated with sternal wound infection, and the lack of evidence that bilateral IMA grafting has a beneficial effect on long-term survival, use of this procedure in high-risk patients is not advisable unless no other suitable conduits are available.

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HLA Histocompatibility Affects Cardiac Transplant Rejection and May Provide One Basis for Organ Allocation

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Prospective human lymphocyte antigen (HLA) typing is not performed for heart transplantation, and the relation between HLA matching and cardiac graft rejection is unclear. Recipient and donor HLA matching were analyzed retrospectively in 51 patients undergoing orthotopic cardiac transplantation. Immunosuppression was based on cyclosporine and prednisone. During the mean follow-up of 34 months (range, 16 to 63 months), the 46 operative survivors had an average of 3.95 rejection episodes (range, zero to 11 episodes). Twenty-one patients had steroid-resistant rejection requiring treatment with polyclonal or monoclonal antithymocyte globulin. Human lymphocyte antigen typing was available for 44 patients, and antigens were grouped in broad specificities. Patients with two or more HLA-A or HLA-B matches had a reduced number of rejection episodes (3/10 versus 19/34) and a lower incidence of steroid-resistant rejection (1/10 versus 18/34; $p = 0.01$). Inclusion of HLA-DR matches did not alter the findings. There was a strong correlation between the increased frequency of rejection and the incidence of steroid-resistant rejection ($p < 0.0001$). Four of six late deaths occurred in patients with steroid-resistant rejection; four were due to acute rejection and two to graft atherosclerosis. Although not currently done, prospective HLA matching is feasible with present typing methods. Our results suggest a rationale for prospective histocompatibility testing in cardiac transplantation with allocation of donor hearts to patients with two or more HLA matches.

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Since the introduction of cyclosporine, cardiac transplantation has become an accepted therapy for end-stage cardiac dysfunction. Cardiac transplant recipient survival during the first year after transplantation approaches 90% [1–3]. However, rejection remains a major cause of morbidity and death. Rejection has been implicated as the cause of death in 30% to 50% of late deaths [4–6]. In other fields of organ transplantation, attention has focused on the impact of the human lymphocyte antigen (HLA) system on graft survival and rejection. A number of large multicenter studies have demonstrated that class I and class II HLA mismatching plays a dominant role in determining long-term renal allograft survival [7,8], and this result has justified organ allocation based on histocompatibility testing. In contrast, little is known about the influence of HLA matching on results of cardiac transplantation although preliminary data (unpublished) from the collaborative study coordinated by Opelz in Heidelberg suggest a relation between matching and survival.

For editorial comment see page 177.

In an attempt to determine the importance of HLA histocompatibility, we retrospectively examined the effect of HLA-A, HLA-B, and HLA-DR matches and mismatches on cardiac transplant survival and the incidence of rejection. We also examined the incidence of steroid-resistant rejection, that is, histological rejection not responding to a steroid pulse and requiring polyclonal antithymocyte globulin or OKT3 monoclonal antibody. In our series, HLA matches affected the incidence of rejection and steroid-resistant rejection. Because HLA typing of donors can now be accomplished in less than six hours [9], our results suggest a rationale for prospective histocompatibility testing with allocation of donor hearts to patients with two or more HLA matches.

Material and Methods

Between February 1984 and February 1988, 51 orthotopic cardiac transplantations were performed at Brigham and Women's Hospital. The mean age of the recipients was 39.6 years. No early deaths were due to rejection. Thirty-day mortality was 10% (5/51). Causes of early death included multisystem organ failure (2 patients), right heart failure, arrhythmia, and pancreatitis (1 patient each), and death occurred on postoperative day 0 to day 27 (mean, day 15).

Patients discharged from the hospital were followed for a mean of 34 months. During this interval, recipients were treated for zero to 11 episodes of rejection (mean, 3.95 episodes). There were six late deaths, occurring 1 to 46 months (mean time, 8 months) postoperatively. Four late deaths were due to rejection and 2 to graft atherosclerosis.

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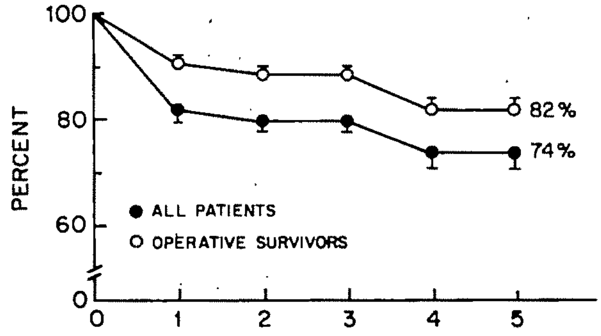

Fig 1. Actuarial probability of survival for all patients and for patients surviving 30 days and discharged from the hospital (operative survivors).

Actuarial survival at 5 years was 74% for all patients and 82% for patients discharged from the hospital (Fig 1).

Donor-recipient pairs were selected on the basis of size and ABO blood group compatibility. Also, a lymphocyte crossmatch was used if preoperative screening indicated greater than 10% sensitization to a random panel. Immunosuppressive therapy consisted of cyclosporine (serum level, 100 to 200 ng/mL) and prednisone (tapered to 0.15 mg/kg). Azathioprine (1 to 2 mg/kg) was added for patients with azotemia or persistent rejection.

Episodes of rejection, detected by periodic endomyocardial biopsies, were defined as lymphocytic infiltrate plus myocyte necrosis, and were treated with corticosteroid pulse therapy (methylprednisolone, 1 g intravenously for three days). Rejection episodes with persistent myocyte necrosis on follow-up biopsy despite steroid pulses (steroid resistant) were treated with antithymocyte globulin or OKT3 monoclonal antibody. Severe rejection with vasculitis and hemorrhage was treated simultaneously with steroids and either antithymocyte globulin or OKT3. Twenty-one patients had at least one episode of steroid-resistant rejection or severe rejection requiring treatment with antithymocyte globulin.

Complete HLA-A, HLA-B, and HLA-DR data were available for 44 donors and patients. No attempt was made to prospectively match donor-recipient pairs based on HLA histocompatibility. For purposes of tabulating HLA matches and mismatches, the A, B, and DR antigens were grouped into broad specificities (Table 1) [10]. An antigen present in both donor and recipient was considered a match, and an antigen present in the donor and not in the recipient was considered a mismatch. The study population was stratified into the following groups: 0 to 1 or 2 to 3 HLA-A and HLA-B matches and 0 to 1 or 2 to 3 HLA-A, HLA-B, and HLA-DR matches. Similarly, the patients were grouped into 0 to 2 or 3 to 4 HLA-A and HLA-B mismatches and 0 to 3 or 4 to 6 HLA-A, HLA-B, and HLA-DR mismatches. Patients were also segregated based on the occurrence of three or fewer or more than three rejection episodes.

Correlations were examined by the Wilcoxon test, the Fisher exact test, or the Mantel-Haenszel χ^2 test. Significant differences were considered to exist when calculated p values were less than 0.05.

Table 1. Human Lymphocyte Antigen Specificities

Broad Specificities	Cross-reacting Antigens
A Locus	
A1	Aw36
A2	A28, Aw68, Aw69
A3	A11
A9	A23, A24
A10	A25, A26, Aw34, Aw43, Aw66
Aw19	A29, A30, A31, A32, Aw33
B Locus	
B5	B51, Bw52
B7	Bw73
B8	Bw59
B12	B44, B45
B13	. . .
B14	Bw64, Bw65
B15	Bw62, Bw63, B15.3
B16	B38, B39
B17	Bw57, Bw58
B18	. . .
B21	B49, Bw50
Bw22	Bw42, Bw54, Bw55, Bw56
B27	. . .
B35	Bw53
B37	. . .
B40	Bw60, Bw61
Bw41	Bw47, Bw48
Bw46	. . .
Bw67	. . .
Bw70	Bw71, Bw72
Bw71	. . .
Bw72	. . .
Bw73	. . .

Results

The relationship between HLA matching and cardiac transplant rejection is shown in Table 2. Frequent (more than three) rejection episodes were associated with fewer

Table 2. Human Lymphocyte Antigen Matching and Frequency of Rejection

No. of HLA Matches	Three Rejections or Fewer	More Than Three Rejections
A and B		
0 or 1	15	19
2	7	3[a]
A, B, and DR		
0 or 1	10	15
2 or 3	12	7[b]

[a] Significance: $p = 0.104$ by Mantel-Haenszel χ^2 test. [b] Significance: $p = 0.153$ by Mantel-Haenszel χ^2 test.

HLA = human lymphocyte antigen.

Table 3. Human Lymphocyte Antigen Matching and Steroid-Resistant Rejection

No. of HLA Matches	No Rejection	Rejection
A and B		
0 or 1	16	18
2	9	1[a]
A, B, and DR		
0 or 1	10	15
2 or 3	15	4[b]

[a] Significance: $p = 0.01$ by Mantel-Haenszel χ^2 test. [b] Significance: $p = 0.009$ by Mantel-Haenszel χ^2 test.

HLA = human lymphocyte antigen.

HLA-A and HLA-B matches and HLA-A, HLA-B, and HLA-DR matches, although the differences were not significant ($p = 0.104$ and $p = 0.153$, respectively). No significant relationship was found between HLA mismatching and the incidence of rejection.

The number of HLA matches did correlate with the incidence of steroid-resistant rejection (Table 3). Steroid-resistant rejection occurred in 18 of 34 patients with 0 or 1 HLA-A and HLA-B matches but only 1 of 10 with 2 such matches ($p = 0.01$). Similarly, steroid-resistant rejection occurred in 15 of 25 patients with 0 or 1 HLA-A, HLA-B, and HLA-DR matches as opposed to 4 of 19 wih 2 or more ($p = 0.009$). In comparison, HLA mismatching was not associated with an increased incidence of steroid-resistant rejection.

There was a strong correlation between the incidence of steroid-resistant rejection and the frequency of rejection episodes (Table 4). Steroid-resistant rejection occurred in 19 of 20 patients with more than three rejection episodes but in only 4 of 26 with three or fewer instances of rejection ($p < 0.0001$).

There was no significant correlation between HLA matching and survival, but 4 of the 6 patients dying late had sustained at least one episode of steroid-resistant rejection. No other variable examined, including age and sex, had any effect on survival or incidence or severity of rejection.

Comment

Despite progress in transplant survival associated with the use of cyclosporine, the role of HLA class I and class II antigen compatibility in cardiac transplant rejection and survival is poorly defined and plays no role in organ allocation. Human lymphocyte antigen histocompatibility clearly does affect results of renal transplantation, and kidneys from cadaveric donors are preferentially transplanted in well-matched recipients.

In renal transplantations, studies have focused on HLA mismatching and graft survival. Takiff and co-workers [8] showed a 5% renal allograft survival advantage in patients with no HLA-A and HLA-B mismatches. Similarly, Opelz [7] noted a 10% allograft survival advantage with no HLA-A and HLA-B mismatches. The role of HLA-DR histocompatibility remains controversial. Both Takiff [8], Opelz [7], and their associates have demonstrated increased renal allograft survival in cyclosporine-treated recipients with no HLA-A and HLA-B mismatches. Although several studies [11, 12] have suggested that the deleterious effects of HLA-DR mismatching are negated with the use of cyclosporine, prospective tissue typing including HLA-DR matching remains an important determinant of organ allocation in renal transplantation.

In our review of patients with cardiac transplants, there was an association between HLA matching and the frequency of graft rejection but significance was not reached. Frist and colleagues [10] reviewed the experience at Stanford, and were also unable to demonstrate any relationship between HLA matching and transplant rejection, although an impact on survival and incidence of infection was seen. As noted, preliminary data from the collaborative heart transplant study (Opelz) suggest that HLA matching may have the same impact on results of cardiac transplantation as has been observed in patients with renal allografts from cadaveric donors.

In our study, HLA-A and HLA-B matching and HLA-A, HLA-B, and HLA-DR matching correlated with the incidence of more serious steroid-resistant rejection. In addition, patients who had at least one episode of steroid-resistant rejection usually had an increased number of rejection episodes and were at increased risk of rejection-related late death. This analysis was based on HLA histocompatibility defined by grouping antigens in broad specificities. The heterogeneity of antigenic loci within a single broad specificity and antigenic heterozygosity were not considered.

This study suggests that HLA-A and HLA-B matches and HLA-A, HLA-B, and HLA-DR matches are associated with a decreased incidence of steroid-resistant rejection in cardiac transplant patients using cyclosporine and steroid immunosuppression. Prospective HLA matching of heart donors and recipients can be accomplished in a matter of hours as has been the practice with lymphocyte cross-matches. The reagents and techniques required to perform HLA matching should be familiar to tissue-typing laboratories affiliated with most large organ-procurement agencies. Typing can be done on donor tissue or even blood and need not be carried out in the donor hospital, just as lymphocyte cross-matching and HLA typing for kidney allocation are performed in centralized tissue-typing laboratories. Our results suggest a rationale for organ allocation based on HLA matching and, especially as techniques of myocardial preservation improve, truly national sharing of hearts for transplantation.

Table 4. Steroid-Resistant Rejection and Frequency of Rejection

Steroid-Resistant Rejection	More than Three Rejections	Three Rejections or Fewer
Present	19[a]	4
Absent	1	22

[a] Significance: $p < 0.0001$ by Fisher's exact test.

We thank Elizabeth Allred, MS, for assistance with the statistical analysis.

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DISCUSSION

DR JACK G. COPELAND (Tucson, AZ): I congratulate DiSesa and associates for raising again the issue of tissue typing in cardiac transplantation, where currently ABO compatibility is most often the only matching.

There is no doubt that a biological relationship exists between goodness of matching for human lymphocyte antigens (HLA) and survival after solid organ transplantation. Of the class I antigens (polypeptides), which are located on the surfaces of all nucleated cells, those produced by the A and B loci evoke strong immune responses including formation of antibodies and cytotoxic T cells.

Class II antigens, glycoproteins found on B lymphocytes, monocytes, endothelial cells and Langerhans cells (of the skin), are produced by the D locus and are felt to play a most important role in rejection by activating T helper cells.

Current immunosuppressive therapy tends to neutralize this relationship of HLA matching to success. We have analyzed HLA class I matching (for A and B antigens) in 146 consecutive patients treated with rabbit antithymocyte globulin induction, followed by triple therapy consisting of cyclosporine, azathioprine, and prednisone, and found an insignificant trend toward improved freedom from rejection and a small (5%) but significant ($p < 0.05$) improvement in survival, but no improvement in freedom from death from rejection and a possibly significant ($p < 0.10$) improvement in freedom from infection (27% at 6 months, 16% at 1 year, 10% at 2 years). We would therefore consider the present HLA matching advantage to be small at best.

DiSesa and associates have shown a reduction in steroid-resistant rejection and a reduction in the number of recipients with over three rejection episodes with retrospective matching. It must be pointed out that the weaker the immunosuppressive regimen, the more likely HLA matching has a favorable effect. For instance, with our immunosuppressive protocol, which would be considered stronger, the survival at 1 year was 94% for all patients, compared with 80% in the report by DiSesa and associates, and we have seen very few steroid-resistant rejections in over 150 consecutive patients. Our mean number of rejections has been 1.24 per patient at 1 year and 1.27 per patient at 3 years, compared with 3.95 episodes per patient at 32 months in the study by DiSesa and associates.

Dr DiSesa, do you think donor sharing based on HLA matching is worthwhile, assuming that a stronger immunosuppressive protocol than yours is in effect? I would ask you to be a little bit more specific than you were in your concluding statement about the tremendous limitations of time, potential recipient acuity, donor availability, geography, and our crude techniques of long-term cardiac preservation, not to mention problems in communication and, in some cases, unhealthy competition. What new information or developments might lead to sharing of transplants based on HLA matching?

DR DiSESA: I appreciate Dr Copeland's comments. He has certainly made a number of contributions to this field.

His comments about our incidence of rejection are well-taken. There is always a balance in this area between the level of immunosuppression, rejection, and infection. We have a very low incidence of infection in our patients; in fact, in our series, which is now 95 patients, only 1 patient has died with infection as the primary cause. Certainly, you will see less rejection if you intensify the immunosuppressive regimen. In fact, in our later patients, we do use triple therapy based on long-term data that are available.

I do not have any data to answer the question of whether a strong immunosuppressive regimen will mitigate the impact of HLA matching. I would turn it around to say that with better HLA matching immunosuppression need not be as strong, and therefore patients may not suffer the infectious complications that inevitably will ensue with more profound immunosuppression.

The time limits that I referred to really concern how long we can store organs before revascularizing them. There are experimental techniques including autoperfusion or other methods that are presently too cumbersome, I think, for widespread use.

The logistics of doing HLA tying are similar to the logistics of lymphocyte cross-matching, which is done routinely in many centers. Therefore, the time limitations are within the span that we presently use, so that if we were set up to do pretransplant HLA typing, it could be done. I think the problem, though, is in identifying all the potential recipients who might be candidates for an HLA-typed heart and then getting the heart transported to a matched patient in a timely fashion. If, as in renal transplantation, it were possible to harvest the heart, do the typing while the heart is in storage, then direct it to the best match, then it would be worth addressing the logistical problems. I certainly would not advocate setting it up until we had more definitive evidence that HLA matching is really going to have a substantial impact, but I think it is important to address this issue in an ongoing fashion.

Notice From the Southern Thoracic Surgical Association

The Thirty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at the Hyatt Regency Cerromar Beach, Puerto Rico, November 8–10, 1990. There will be a $155 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 8, 1990. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1990, to Donald C. Watson, Jr, MD, Program Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office or in the March 1989 issue of *The Annals of Thoracic Surgery*. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1990 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1990, and forwarded to Lenox Baker, Jr, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601.

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Dynamic Aortomyoplasty to Assist Left Ventricular Failure

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The efficacy of skeletal muscle contractile force to augment left ventricular function has been demonstrated experimentally and clinically by the cardiomyoplasty procedure. Another approach in biomechanical cardiac assistance is the use of electrostimulated skeletal muscle in an extracardiac position. We describe an autologous counterpulsating device using the native ascending aorta as a ventricular chamber wrapped by an electrostimulated latissimus dorsi muscle flap (LDMF). This model avoids thrombotic complications observed in skeletal muscle neo-ventricles associated with prosthetic chambers. In 8 goats, a right LDMF was transferred to the thoracic cavity by removal of the second rib. In 4 goats, the diameter of the aorta was enlarged by surgical implantation (using lateral clamping) of an autologous pericardial patch. The LDMF was wrapped around the ascending aorta and electrostimulated using an external diastolic pulse generator connected to a sensing myocardial lead and to LDMF pacing electrodes. Hemodynamic studies were performed (left ventricular, aortic, and pulmonary artery pressures and rate of rise of left ventricular pressure). The LDMF diastolic counterpulsation was performed using a burst of 30 Hz, with a delay from the R wave adjusted to provide optimal diastolic augmentation. Percent increase in the subendocardial viability index was calculated during unassisted and assisted cardiac cycles (1:2) at baseline and after acute heart failure induced by the administration of high doses of propranolol hydrochloride (3 mg/kg intravenously). Diastolic aortic counterpulsation by the stimulated LDMF resulted in a significant improvement in the subendocardial viability index both at baseline and after induced cardiac failure in both groups, though the increase was greater in the group with aortic enlargement.

(Ann Thorac Surg 1990;49:225–30)

Aortomyoplasty is a surgical procedure that consists of wrapping a latissimus dorsi pedicled muscle graft around the ascending aorta to compress it, with synchronous electrostimulation of the muscle mass in each diastole. The native ascending aorta, enlarged by an autologous pericardial patch, becomes a ventricular chamber. This model of assisted circulation avoids thrombotic complications and systemic emboli observed in skeletal muscle neo-ventricles associated with prosthetic chambers [1–4]. With dynamic aortomyoplasty, the autologous "neo-ventricle" is continuously washed out by the left ventricular (LV) output.

Skeletal muscle plasticity and adaptive changes is the basic physiological concept of biomechanical assist devices. The efficacy of skeletal muscle contractile force to augment LV function has been documented experimentally and clinically using the cardiomyoplasty procedure [5–7]. Electrical induction of fatigue resistance in skeletal muscles may also be effective for long-term circulatory assistance using diastolic counterpulsation.

With the aortomyoplasty procedure, we are seeking an extracardiac biomechanical assist device for hearts with contraindications to performance of the cardiomyoplasty technique (extremely dilated cardiomyopathies, previous cardiac operations, hypertrophic cardiomyopathies) or for use in conjunction with LV cardiomyoplasty. We report here the preliminary experimental results of dynamic aortomyoplasty in animal models with acute heart failure.

Material and Methods

Eight adult alpine goats weighing 36 to 45 kg were used. Anesthesia was induced with an intramuscular injection of 2% xylazine and maintained with intravenously administered alfaxalone-alfadolone acetate. Curariform drugs were contraindicated.

All goats underwent a right vertical, lateral thoracic incision to facilitate dissection of the latissimus dorsi muscle. The right latissimus dorsi muscle was divided from its insertion on the lateral aspect of the last four ribs, iliac crest, and thoracolumbar fascia, and was mobilized proximally as a pedicled flap. Pacing electrodes were implanted (two leads, model SP 5528; Medtronic, Maastricht, the Netherlands) into the proximal part of the latissimus dorsi muscle flap (LDMF), which was brought into the chest through an opening made by resecting a portion of the second rib [8]. Care was taken to preserve the neurovascular bundle.

Sternotomy was performed. The ascending aorta, the

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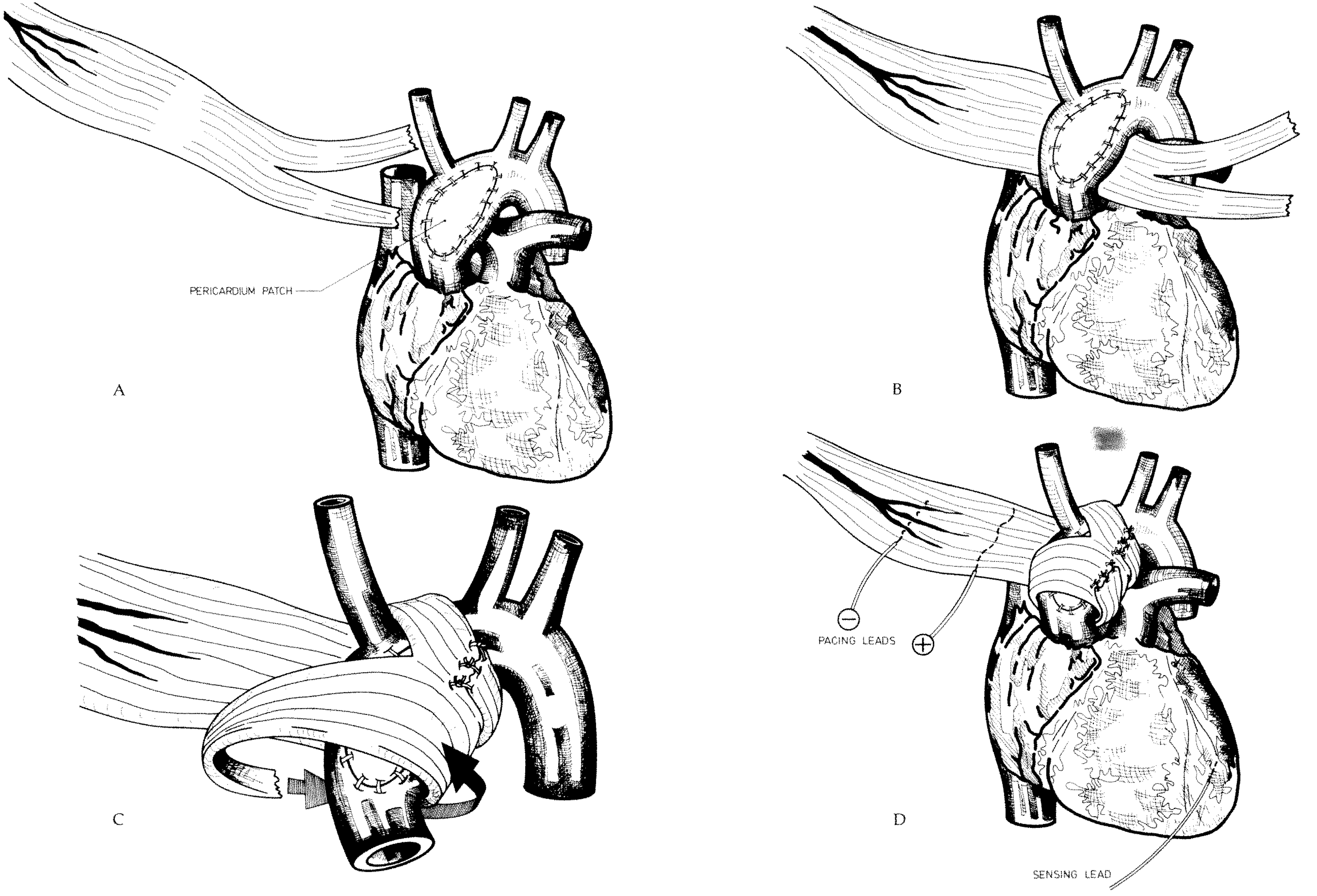

Fig 1. (A) The ascending aorta, the transverse aortic arch, and its branches are dissected. The aorta is enlarged by implantation of a patch of autologous pericardium. (B) The latissimus dorsi muscle flap (LDMF), its distal end split longitudinally, is positioned behind the aorta. (C) The aorta is wrapped with the LDMF in a counterclockwise fashion. (D) The aorta is covered on both sides of the brachiocephalic trunk. Muscle fibers lie perpendicular to the longitudinal axis of the aorta.

transverse aortic arch, and its branches were dissected (Fig 1A). In 4 goats, the ascending aorta was enlarged by implantation of an elliptical patch of autologous pericardium treated with glutaraldehyde [9]. This was done by side-clamping the aorta and placing a continuous suture of polypropylene monofilament 5-0.

In all animals, LDMF was positioned behind the aorta (Fig 1B). Then the ascending and transverse aorta was wrapped with the muscle flap in a counterclockwise fashion so that its fibers lay perpendicular to the longitudinal axis of the aorta (Fig 1C). To cover the aorta on both sides of the brachiocephalic trunk, the distal end of the LDMF was split longitudinally (Fig 1D), with care taken to consider its intramuscular neurovascular anatomy [10, 11].

Skeletal muscle electrostimulation was performed using an external counterpulsator (Medtronic model SP 3076) connected to a sensing myocardial lead (Medtronic model SP 5548) and to LDMF pacing electrodes. The variables involved in muscle stimulation were as follows: pulse amplitude, 4 to 6 V; pulse width, 210 μs; burst rate, 30 Hz; and burst duration, 185 ms. Diastolic counterpulsation was performed using a delay from the R wave adjusted to provide optimal diastolic augmentation. Short-term cyclic skeletal muscle electrostimulation (ten minutes per cycle) was delivered to allow functional study of dynamic aortomyoplasty.

The following hemodynamic studies were performed: measurement of LV, aortic, and pulmonary artery pressures and rate of rise of left ventricular pressure. The extent of diastolic augmentation was measured by the subendocardial viability index: diastolic pressure–time index/systolic tension–time index [12, 13]. Percent increase in this ratio (diastolic pressure–time index/systolic tension–time index) was calculated during unassisted and assisted cardiac cycles (1:2) at baseline and after acute heart failure induced by high-dose propranolol hydrochloride (3 mg/kg intravenously). The subendocardial viability index was derived from superimposed tracings of aortic arch and LV pressures.

Statistical analysis was performed using the paired *t* test and analysis of variance. Data are reported as the mean ± the standard deviation. A *p* value of less than 0.05 was considered significant.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Results

Experimental results were obtained in the acute phase. Early electrostimulation was performed while muscle conditioning, collateral vascular supply, and LDMF adhesion to the aorta did not exist. As expected, muscle fatigability occurred four to six minutes after induction of stimulation.

The diameter of the ascending aorta was 14.5 ± 2 mm, and its perimeter was 45.5 ± 3 mm. The surface area of the pericardial aortic patch used in 4 goats was 260 ± 30 mm^2. The length of the aortic segment wrapped by the LDMF was 70 ± 8 mm.

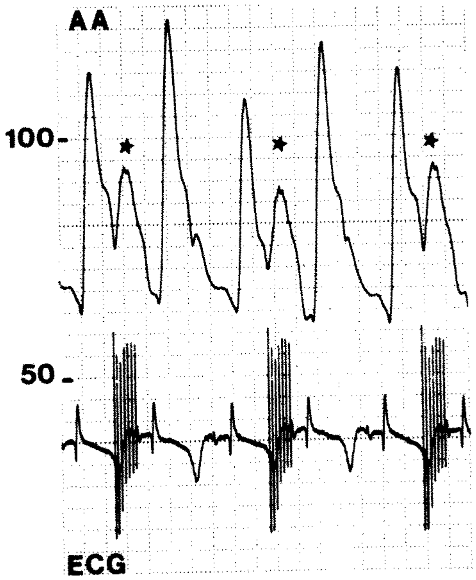

Fig 2. Hemodynamic recording after dynamic aortomyoplasty. Ascending aortic (AA) pressure at baseline. The stars mark diastolic augmentation in assisted cycles. Heart-to-muscle contraction ratio was 2:1. (ECG = electrocardiogram.)

The average peak ascending aortic pressure generated by dynamic aortomyoplasty under baseline conditions was 90 mm Hg (systemic blood pressure, 115/65 mm Hg) (Fig 2). In the 4 goats with aortic enlargement, the average peak pressure during LDMF stimulation was 105 mm Hg (systemic pressure, 105/70 mm Hg) (Fig 3).

The hemodynamic data are shown in Tables 1 and 2. Diastolic aortic counterpulsation by the stimulated LDMF resulted in a significant increase in the subendocardial viability index both at baseline (+29.3%) (Fig 4) and after

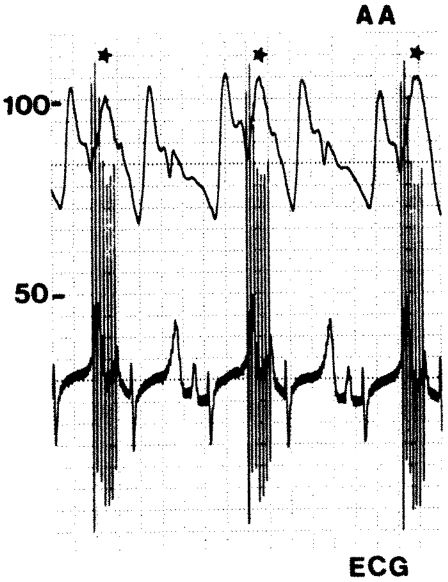

Fig 3. Diastolic augmentation (stars) after enlargement of the ascending aorta (AA). (ECG = electrocardiogram.)

Table 1. Increase in Subendocardial Viability Index With Dynamic Aortomyoplasty Diastolic Augmentation on Alternate (Heart-Muscle Stimulation Ratio, 2:1) Cardiac Cycles

	Control		Cardiac Failure	
Animal No.	Without Stimulation	With Stimulation	Without Stimulation	With Stimulation
1	0.95	1.35	0.98	1.40
3	0.88	1.22	0.86	1.25
6	1.18	1.29	1.08	1.38
7	0.82	1.32	0.84	1.32
2	1.02	1.40	1.05	1.31
4	1.05	1.38	0.99	1.33
5	0.98	1.18	0.95	1.20
8	1.11	1.42	1.00	1.22
Mean	0.998	1.322[a]	0.968	1.301[b]
Standard deviation	0.117	0.086	0.084	0.072

[a] Paired t test (two-tailed): degrees of freedom = 7, $t = -7.339$, $p < 0.001$ versus without stimulation. [b] Paired t test (two-tailed): degrees of freedom = 7, $t = -10.283$, $p < 0.001$ versus without stimulation.

induced cardiac failure (+26.8%). In the group with aortic enlargement, the average increase in the index was +35.8% and +42.2%, respectively.

During these experiments, we noted that the electrostimulated LDMF contracted vigorously. Its mechanical action over the aorta resulted in a homogeneous "systolic activity." No displacement of or angularities in the aortic arch and no aortic valve regurgitation were observed.

Despite the fact that heparin sodium was not used during these experiments, no thrombus was noted in the aortic chambers.

Table 2. Increase in Subendocardial Viability Index in Animals With Aortic Enlargement

	Control		Cardiac Failure	
Animal No.	Without Stimulation	With Stimulation	Without Stimulation	With Stimulation
1	0.95	1.35	0.98	1.40
3	0.88	1.22	0.86	1.25
6	1.18	1.29	1.08	1.38
7	0.82	1.34	0.84	1.32
Mean	0.957	1.300[a]	0.940	1.337[b]
Standard deviation	0.157	0.059	0.112	0.067

[a] Paired t test (two-tailed): degrees of freedom = 3, $t = -3.980$, $p < 0.005$ versus without stimulation. [b] Paired t test (two-tailed): degrees of freedom = 3, $t = -10.6$, $p < 0.005$ versus without stimulation.

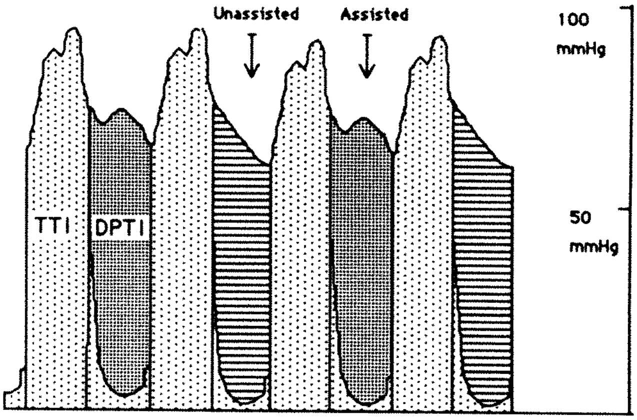

Fig 4. Increase in subendocardial viability ratio (diastolic pressure–time index [DPTI]/systolic tension–time index [TTI]), during assisted cycles after dynamic aortomyoplasty (experiment 8).

Comment

Thirty-five thousand people per year in the United States need replacement of irreparable, sick natural hearts [14]. Because no more than 2,000 donor hearts will be available, 33,000 artificial hearts will be necessary on a permanent basis, on top of the few hundred needed as a bridge to transplantation. None of the available treatments of severe cardiac failure can be expected to benefit a large number of patients in the near future. Physicians must search for alternative techniques [15–17].

We have been investigating the use of the patient's own skeletal muscle to augment myocardial performance. Latissimus dorsi dynamic cardiomyoplasty has demonstrated experimentally and clinically its capacity to improve ventricular function on a long-term basis [5, 6].

The aim of dynamic aortomyoplasty is to create a new hemocompatible contractile chamber in the ascending aorta using an autologous pericardial patch to enlarge its diameter. The electrostimulated LDMF is wrapped around the neo-chamber. The native aortic valve serves to close its afferent orifice, and hemodynamically this biological device acts as a new ventricle and the impaired left ventricle functionally becomes a left atrium. Therefore, LV afterload decreases and counterpulsation is effectively performed at the proximity of the coronary artery ostia.

One of the advantages of dynamic aortomyoplasty is that it is performed without heart manipulation, aortic cross-clamping, or cardiopulmonary bypass. Moreover, contrary to another experimental model of muscular wrapping of the descending aorta [15], dynamic aortomyoplasty avoids the risk of paraplegia due to spinal cord ischemia.

Results obtained with the model of dynamic aortomyoplasty associated with induced cardiac failure showed that when the aorta is enlarged the increase in subendocardial viability index is larger than when the aorta is left intact. This means that a dilated ventricle is better assisted by a larger aortic chamber volume. In patients with a large and long ascending aorta, it probably is not necessary to use patch enlargement of the aorta or to split the distal end of the LDMF, wrapping entirely the aorta before the origin of the brachiocephalic trunk. Aortic valve regurgitation, Marfan's syndrome, and a calcified ascending aorta could be contraindications to dynamic aortomyoplasty. Routine preoperative computed tomographic scanning and nuclear magnetic resonance imaging are indicated to detect aortic calcifications in candidates before operation. On a hypothetical basis, dynamic aortomyoplasty can be viewed as a complementary technique in patients who have undergone LV cardiomyoplasty and in whom supplementary hemodynamic support is necessary.

The extensive experience with the intraaortic balloon pump demonstrates considerable hemodynamic and physiological benefits of diastolic counterpulsation to the failing heart [18]. Efforts were made to reproduce these effects using extraaortic ventricles wrapped with electrostimulated muscles [19], but were always limited by the thromboembolic potential of the prosthetic chambers because of interactions between the blood and artificial surfaces. Dynamic aortomyoplasty offers advantages similar to those of the intraaortic balloon pump. Moreover, because no prosthetic materials are used and blood flow is continuous, stasis and turbulence are avoided; hence no thromboembolic events are encountered. Consequently, the procedure could be viewed as a potential permanent perivascular assist device.

Although short-term experimental dynamic aortomyoplasty led to significant diastolic augmentation, a long-term study using this procedure will allow us to evaluate the hemodynamic and functional effects of this biomechanical assist device to support chronic ventricular failure. The muscle we mobilized loses some of its blood supply, and we assume there is limited contractile function postoperatively. However, after a certain delay (2 weeks), sufficient blood flow will be reestablished by means of collateral circulation, and muscle function will recover. It is also important to consider the postoperative muscle training. Skeletal muscle receiving long-term electrostimulation undergoes metabolic transformation (glycolytic toward oxidative), with induction of fatigue resistance [20, 21].

Before dynamic aortomyoplasty can be used in the clinical setting, upcoming experimental studies should answer three major questions. (1) What are the effects of long-term diastolic counterpulsation? (2) How do the local (aortic) and systemic circulations adapt to and tolerate dynamic aortomyoplasty? (3) What are the hemodynamic benefits of the procedure? We think these questions are partially clarified by the circulatory system of the kangaroo [22]. In this animal, the ascending aortic pressure waveform displays a very large secondary wave that begins in late systole or early diastole and continues throughout most of diastole. The peak of this secondary wave (which almost always occurs in diastole) is often greater than systolic peak pressure and results apparently from intense wave reflections from peripheral vascular beds in the lower part of the kangaroo's body. These findings are explicable on the basis of body size and shape and the extreme eccentric location of the heart within the body. This permanent physiological counterpulsation system is very well tolerated and assists chronically the voluminous lower part of the kangaroo's body.

Long-term experimental studies involving dynamic aortomyoplasty will elucidate the potential and clinical feasibility of this new, promising approach to biomechanical assisted circulation.

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DISCUSSION

DR ADRIAN KANTROWITZ (Detroit, MI): It might be of some value to point out that we have done similar experiments and reported them about 25 years ago. A series of experiments was done in our laboratory in Brooklyn by Dr Nosé in which he demonstrated essentially the same thing, that the closer you make a counterpulsating device to the aortic valve, the more effective it is. The second thing that we did was to wrap a leaf of the diaphragm around the thoracic aorta and stimulate it in a counterpulsation mode. We had results that were not too different from those of Chachques and associates.

The reason that we abandoned that approach was twofold: (1) we were not able to figure out how to overcome the fatigue problem, and (2) the stroke of that ventricle around the descending thoracic aorta was too small—it was about 3 or 4 mL.

I would be interested to ask the question, first, do you know what the stroke volume of your aortic wrap device is? And, second, you implied that you felt it had better effects because it was closer to the coronary ostia. I would have to respectfully disagree with that. I think it has no relationship to how close it is to the coronary ostia. The flow during diastole through the left coronary artery is totally dependent on the pressure, or on the difference between intramyocardial pressure and aortic pressure.

Nevertheless, I think this is a very nice piece of work and I congratulate you.

DR CHACHQUES: We know very well the preliminary work by Dr Kantrowitz that opened the door for these kind of biological assist devices. Our choice of the ascending aorta myoplasty instead of the descending aorta was, first, to avoid paraplegia due to spinal cord ischemia, and, second, because the diameter of the ascending aorta and hence the volume of blood counterpulsated were more important. On the other hand, as you have mentioned earlier, Dr Nosé and others have demonstrated that the closer you make a counterpulsation device to the aortic valve the more effective it is and the higher peak pressure wave you therefore obtain. Consequently the coronary circulation, which is directly proportional to the pressure during diastole, will improve if the device is closer to the aortic valve.

Concerning the stroke volume, our hemodynamic studies did not include this variable.

DR JOHN A. JACOBEY (Mountain Lakes, NJ): Dr Chachques, I believe I heard you mention that there was some unloading of afterwork of the left ventricle. I did not see that presented in your graphs. Perhaps there is another graph that shows where left ventricular systolic pressure does indeed come down which, as we all know, is one of the two basic components of counterpulsation, leaving the single effect approaches to be called either diastolic augmentation or systolic unloading.

Again, I appreciate your paper, and I would like to ask what you think your particular device can do to unload the left ventricle.

DR CHACHQUES: To demonstrate the effectiveness of the diastolic augmentation provided by the aortomyoplasty procedure and to demonstrate the decrease in the left ventricular afterload we have used the subendocardial viability index that was derived from superimposed tracings of the aortic arch and left ventricular pressures. It was perhaps a mistake not to show directly a more simple and straightforward assessment of left ventricular pressure. However, if we look at the aortic pressure curves (see Figs 2, 3) we note that muscular relaxation is rapid and acts like balloon deflation in the intraaortic balloon pump. This "diastole" of the aortomyoplasty chamber could explain the decrease in LV afterload.

DR GEORGE J. MAGOVERN (Pittsburgh, PA): Was this a chronic model, and how did you induce chronic congestive heart failure? I think that seems to be a key to evaluating whether this procedure will work over a long period of time. One problem in our work has been the stimulation of the muscle, and we find that it is pretty difficult to thread the electrode through and get a uniform distribution of the current with uniform contractions. We have been putting the electrode on the nerve per se and find that we use much less current and obtain better distribution. But I think you will continue, and you should continue on this, because we have followed muscles that have been stimulated like this now for over 2 years and they do stay viable and biopsies do show that conversion occurs, as you well know. So, I think if you can get a long-term model, then it will be much more effective.

DR CHACHQUES: Our present model was not a chronic one because the implantable diastolic pulse generator was not available at that time. We agree that chronic experiments are necessary. Concerning the skeletal muscle pacing electrodes we respectfully disagree with Dr Magovern as we obtain homogeneous, diffuse, and strong contractions with the electrodes we are using (Medtronic SP 5528) implanted into the muscle very close to the nerve branches. We have demonstrated that irreversible nerve damage, due to compression and fibrosis, may occur if electrodes are placed around the nerve itself.

DR GREGORY A. MISBACH (Seattle, WA): I think that this is a very important frontier to be pursued, but I have one question. One of the limitations of skeletal muscle is lack of left ventricular afterload reduction, because you do not have a rapid deflation of a balloon as you do in an intraaortic balloon device. It also seems that it is the left ventricle that has to reinflate this counterpulsation device, which is your neo-ventricle. Do you think that there is work lost by the left ventricle in distending the ascending aorta and neo-ventricle, and does the compliance of your new aorta have some long-term effect that would influence this?

DR CHACHQUES: Dynamic aortomyoplasty will be a chronic biomechanical support to the irreversibly diseased left ventricle. This sick left ventricle will then act as a left atrium and the enlarged ascending aorta acts as a neo–left ventricle. However if the left ventricular impairment is too serious for the left ventricle to be able to pump the blood to the neo-chamber it would be interesting to consider an associated cardiomyoplasty procedure using the left latissimus dorsi to assist the failing left ventricle.

Computerized Activation Sequence Mapping of the Human Atrial Septum

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Barry H. Branham, MS, Thomas E. Canavan, MD, John P. Boineau, MD,
Michael E. Cain, MD, Peter B. Corr, PhD, and James L. Cox, MD

Division of Cardiothoracic Surgery, Department of Surgery, and Division of Cardiology, Department of Medicine, Washington University School of Medicine, Barnes Hospital, St. Louis, Missouri

To delineate the propagation of electrical activation in the atrial septum, atrial epicardial and atrial septal maps were recorded intraoperatively using a 156-channel computerized mapping system in 12 patients during sinus rhythm (n = 10), supraventricular tachycardia associated with septal pathways in Wolff-Parkinson-White syndrome (n = 3), atrioventricular (AV) node reentrant tachycardia (n = 4), and atrial flutter (n = 5). The epicardial and septal data were recorded simultaneously from 156 atrial electrodes, digitized, analyzed, and displayed as isochronous maps on a two-dimensional diagram of the atria. During sinus rhythm, the activation wave fronts propagated most rapidly along the large muscle bundles of the atrial septum. During supraventricular tachycardia associated with Wolff-Parkinson-White syndrome, the earliest site of retrograde atrial activation usually corresponded to the position of atrial insertion of the septal pathways. However, the earliest site of activation during orthodromic supraventricular tachycardia was different from that during ventricular pacing in 1 patient with a posterior septal accessory pathway localized by the epicardial mapping study. The data document the rationale for dividing the ventricular end of the accessory pathways (ie, the endocardial technique) rather than the atrial end (ie, the epicardial technique) in patients with Wolff-Parkinson-White syndrome. During AV node reentrant tachycardia, atrial activation data suggested that atrial tissue lying outside the confines of the anatomical AV node is a necessary link in this common arrhythmia. Thus, these atrial septal maps explain why surgical dissection, or properly positioned small cryolesions placed in the region of the AV node, can ablate AV node reentrant tachycardia without altering normal AV node function. The maps recorded during atrial flutter suggest the importance of the atrial septum as one limb of a macroreentrant circuit responsible for the arrhythmia, and imply that atrial flutter is amenable to control by surgical techniques. These studies demonstrate the details of normal atrial septal activation, the importance of the atrial septum in a variety of different atrial arrhythmias, and the basis of and potential for surgical ablation of the most common types of supraventricular arrhythmias.

(Ann Thorac Surg 1990;49:231–41)

The atrial septum is a continuous structure of common right and left atrial myocardium, and the atrioventricular (AV) conduction system courses through its inferior rim [1]. Because of its anatomical relationship to the atria and AV node, many types of supraventricular arrhythmias involve the atrial septum. Previous investigators have mapped the atrial septum in animals [2–6] and in patients during preoperative electrophysiological studies [7, 8] or during a cardiac operation [9, 10]. However, these studies were limited in that either a catheter electrode or a single exploring electrode was used. Mapping the atrial septum with a catheter electrode is limited by the number of points that can be mapped, by exact knowledge of the electrode position, and by reliance on a sustained, stable rhythm [11]. These limitations result in a lack of anatomical correlation between different individuals within a study group. Mapping the atrial septum during a cardiac operation using a single exploring handheld electrode has been accomplished during cardiopulmonary bypass, and individual electrograms have been recorded sequentially from multiple sites on the atrial septum [9, 10]. Although exact anatomical positioning is possible, the approach is time-consuming and also requires a stable, sustained rhythm.

Cardiac mapping techniques have been developed for simultaneous multichannel data acquisition and computer-assisted data analysis [12–14] using up to 156 bipolar electrograms recorded from atrial epicardial intraoperative maps [14]. However, the atrial septum was not mapped in those studies. The present report describes a method for activation sequence mapping of both the atrial septum and the atrial epicardium using the same 156-channel computerized system, and describes propagation of electrical activity in the atrial septum during sinus rhythm, atrial and ventricular pacing, and various types of supraventricular arrhythmias.

Presented at the Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons, Baltimore, MD, Sep 11–13, 1989.

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Table 1. Summary of Patient Data

Patient No.	Age (yr)	Sex	Diagnosis
1	26	F	AV node reentry
2	18	F	PJRT (bypass tract in anterior septum)
3	22	F	AV node reentry
4	24	F	AV node reentry
5	12	M	AV node reentry, WPW syndrome (posterior septal pathway)
6	58	M	Atrial flutter/fibrillation
7	18	M	AV node reentry
8	19	M	AV node reentry, Mahaim fiber
9	27	F	AV node reentry
10	12	F	WPW syndrome (posterior septal pathway)
11	28	M	Automatic right atrial tachycardia
12	52	M	Atrial flutter/fibrillation

AV = atrioventricular; PJRT = permanent form of junctional reciprocating tachycardia; WPW = Wolff-Parkinson-White.

Material and Methods

Patient Characteristics

Twelve patients with a variety of supraventricular arrhythmias were studied intraoperatively before definitive surgical treatment of the arrhythmias (Table 1). There were 6 female and 6 male patients ranging in age from 12 to 58 years (mean age, 26 years). Of the 12 patients, 7 had AV node reentrant tachycardia (AVNRT). Two of the patients with AVNRT had other cardiac abnormalities: Wolff-Parkinson-White (WPW) syndrome with a posterior septal pathway and mild Ebstein's anomaly in 1 and ventricular preexcitation due to a Mahaim fiber in the other. Two of the other 5 patients had medically refractory atrial flutter/fibrillation; 1 patient had a permanent form of junctional reciprocating tachycardia with an anterior septal pathway; 1 had WPW syndrome with a posterior septal accessory pathway; and 1 had automatic atrial tachycardia originating in the right atrium.

The indication for surgical intervention in each patient was failure of medical therapy as a result of ineffectiveness or intolerable side effects of the antiarrhythmic drugs. The atrial septum was mapped before surgical treatment in all patients. All procedures were primary operations, and appropriate informed consent was obtained preoperatively from the patients or their parents. There were no operative complications related to the mapping procedure.

Electrode Design

Two types of electrode templates were used to record the activation sequences of the atrial septum. In the first 4 patients, a flat silicone rubber sheet (Silastic, 0.5 mm [0.02 inch] in thickness; Dow Corning) was used (Fig 1, top). Forty-eight bipolar electrodes were incorporated into this septal template. The electrodes were constructed from fine silver wire (quad-Teflon-coated silver wire, 0.125 mm [0.005 inch] in diameter; Medwire, Inc) stripped of its Teflon coating on one end and passed through the silicone rubber sheet forming the electrode template. Each bipolar electrode consisted of two silver-wire contact points located 1 mm apart with an interelectrode distance of 5 mm.

In patients 5 through 12, a molded silicone (Silastic, medical adhesive silicone, type A; Dow Corning) template with 80 bipolar electrodes was used (Fig 1, bottom). The atrial septal electrode patch was fashioned from a plaster

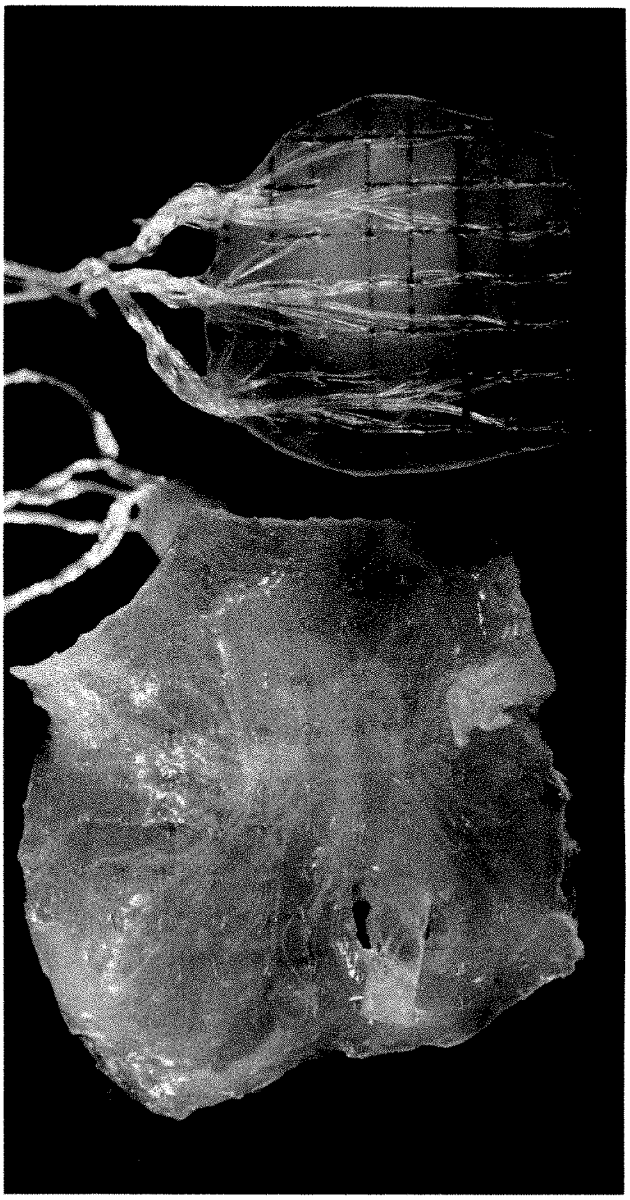

Fig 1. Atrial septal electrode templates with a total of 48 (top) and 80 (bottom) bipolar electrodes. The left upper portion of each template is positioned on the membranous atrioventricular septum. A small rectangular tab on the left upper portion of the bottom template is positioned on the ventricular septum for ventricular reference, and another tab is positioned on the proximal coronary sinus. The hole at the left lower portion of this template is for drainage of blood from the coronary sinus and for anatomical fixation.

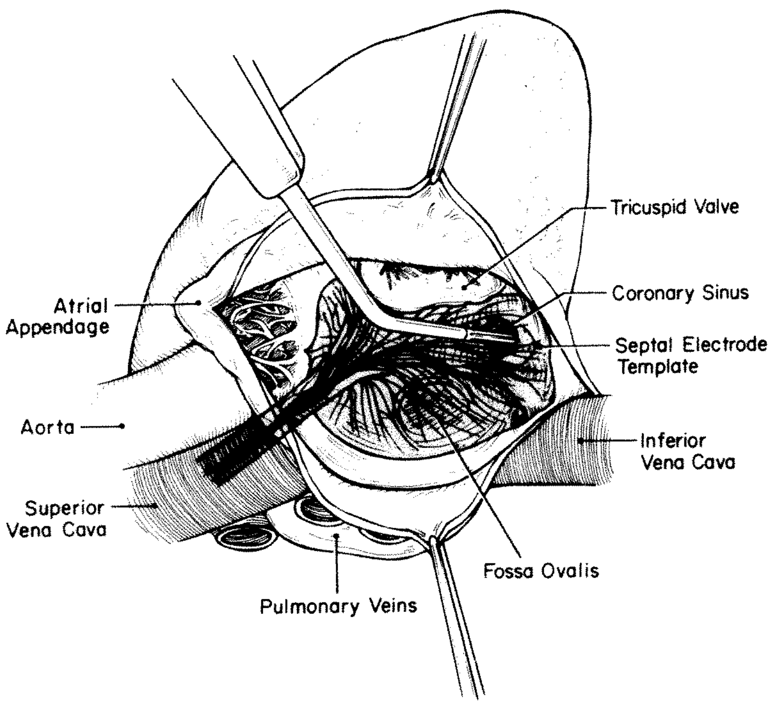

Fig 2. Atrial septal template as seen by the surgeon. A suction tip is inserted into the coronary sinus to aspirate blood and provide anatomical fixation. The template illustrated here is the bottom one in Figure 1.

cast, which was molded to the atrial septal surface of the right atrium using a heart from a human cadaver as a model. A hole on the template was used for aspirating blood from the coronary sinus and provided a fixed anatomical reference point (Figs 2, 3). Two small pieces of silicone rubber sheeting (approximately 5 × 10 mm) were fixed at right angles to the molded template to insert into the coronary sinus and over the AV membranous septum into the ventricle. Electrodes on these "flaps" provided proximal coronary sinus and ventricular electrograms. The 80 bipolar electrodes on this molded template were constructed in the same manner as those on the flat template already described. The bipolar electrodes were also separated by a distance of 5 mm.

Computerized Mapping Procedures

Computerized mapping was performed intraoperatively in each patient after induction of anesthesia, exposure of the heart through a median sternotomy, and cannulation of the great vessels. In 6 patients, the atrial epicardium was mapped before the septum. As described previously [14], a left atrial template containing 44 bipolar electrodes was positioned on the posterior surface of the left atrium beneath the pulmonary veins, and extended from the left atrial appendage to the posterior atrial septum adjacent to the inferior vena cava. A transverse sinus template containing 32 bipolar electrodes was placed posterior to the ascending aorta to contact the medial and anterior surfaces of the superior vena cava and the right and left atria. In 3 of the 6 patients, a right atrial template containing 80 bipolar electrodes was positioned over the lateral surface of the right atrium, and the epicardium was mapped before the atrial septum.

In these studies, computerized atrial epicardial mapping was performed before the initiation of cardiopulmonary bypass except in 1 patient in whom hemodynamic deterioration necessitated institution of bypass. After removal of the lateral right atrial epicardial template and institution of normothermic total cardiopulmonary bypass, a right atriotomy was performed and the atrial septal template was positioned (see Fig 2). Data were

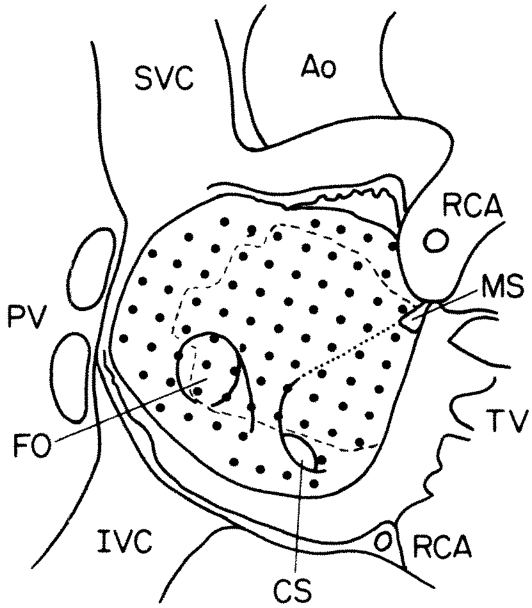

*Fig 3. Relation of electrode positions (*black dots*) to right atrial anatomy. The* broken line *indicates the position of the smaller template in Figure 1. (*Ao *= aorta;* CS *= coronary sinus;* FO *= fossa ovalis;* IVC *= inferior vena cava;* MS *= membranous septum;* PV *= pulmonary veins;* RCA *= right coronary artery;* SVC *= superior vena cava;* TV *= tricuspid valve.)*

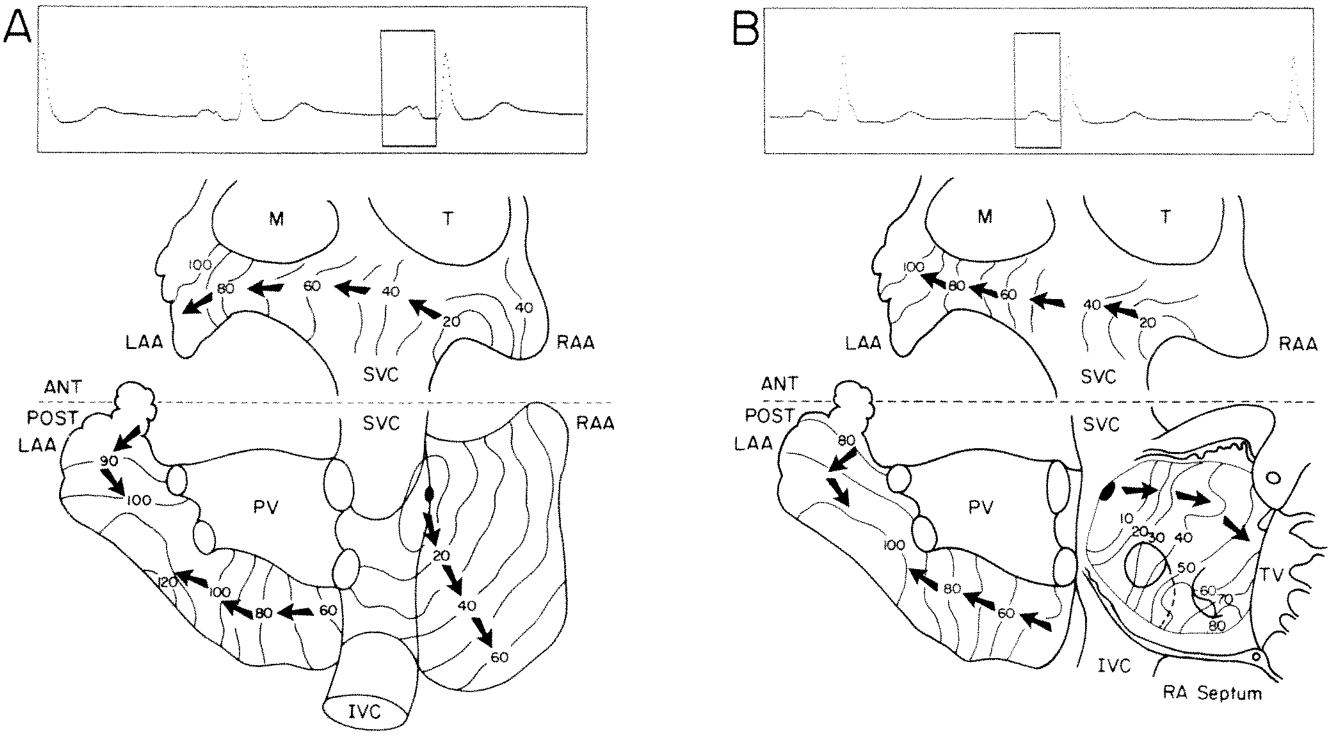

Fig 4. Isochronous atrial epicardial and septal activation sequence maps. (A) Epicardial activation sequence for a single normal sinus beat and a surface lead electrocardiogram. The box around the P wave is the window of data analyzed to produce the activation map. (B) Activation of the atrial septum along with the posterior left atrium and anterior atria during normal sinus rhythm. (ANT = *anterior;* LAA = *left atrial appendage;* M = *mitral valve;* POST = *posterior;* RA = *right atrial;* RAA = *right atrial appendage;* T = *tricuspid valve; other abbreviations the same as in Figure 3.)*

recorded during sinus rhythm, atrial pacing, and ventricular pacing, and during supraventricular tachycardia or atrial flutter/fibrillation.

Data Processing and Analysis

The computer system employed for the acquisition and analysis of atrial electrographic data has been described previously [12, 14, 15]. Bipolar electrograms were individually amplified and filtered from 40 to 500 Hz. The individual electrogram signals were converted from analog to digital form at a sampling rate of 2 kHz with 12 bits of resolution. The digitized signals were then transformed from parallel to serial format for transmission through a fiberoptic cable to the computer facility located approximately 1,500 m from the operating room. The electrographic data were then reconverted from serial to parallel form and stored on a Sangamo-Weston Sabre IV high-density digital tape recorder. Accompanying the 156 channels of digitized data were three channels for simultaneous recording of standard electrocardiographic leads and one channel for voice track recording.

Playback of the electrographic signals from the high-density tape recorder onto the disk of a Digital Equipment MicroVax II computer allowed analysis of the electrographic information. First the surface electrocardiogram was scanned to identify the area of interest. Then a time window was positioned to encompass an entire cycle of atrial activation. The electrograms recorded at each of the 156 bipolar epicardial electrodes during the time frame encompassed by the window were analyzed [15, 16] and displayed serially on a graphic monitor. After visual editing of all electrograms, atrial activation data were displayed with the aid of a Lexidata 3400 color graphics display system. The activation sequence map displayed the time in milliseconds at which the depolarization wave reached each electrode position on a schematic outline of the atrium.

Results

Simultaneous intraoperative computerized mapping accurately and rapidly facilitated the recording of the activation sequence of the atrial epicardium and the atrial septum. The molded template fit well on the atrial septum in every patient even though the size of each heart was different.

Atrial Septal Activation During Normal Sinus Rhythm

Atrial septal activation sequences were determined in 9 patients during sinus rhythm (Fig 4). The wave front of depolarization in Figure 4 is depicted as a series of isochronous lines drawn at 10-ms intervals. During sinus rhythm (Fig 4A), at a cycle length of 924 ms, the earliest activation occurred in the sinoatrial node area at the junction between the superior vena cava and the body of the right atrium. As previously described by Canavan and colleagues [14] and Boineau and associates [17], the activation wave front propagated asymmetrically. The ante-

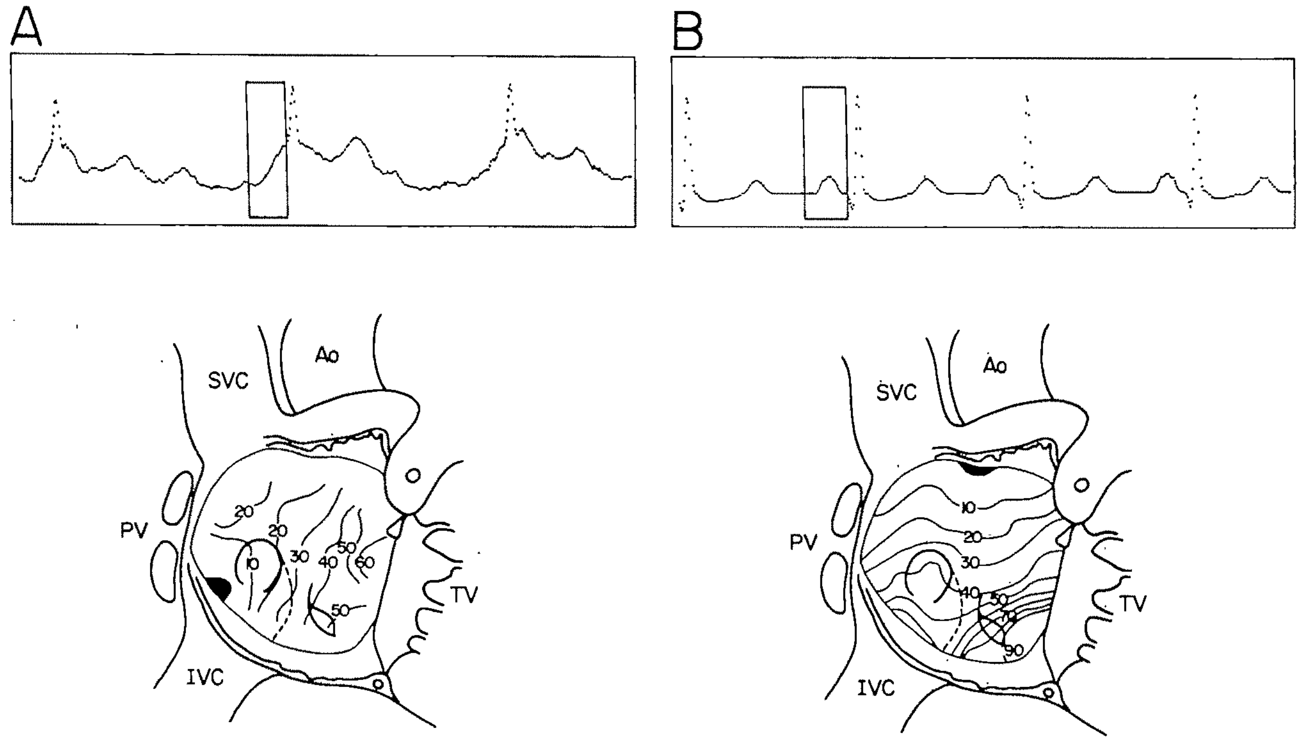

Fig 5. Atrial septal activation during normal sinus rhythm in 2 different patients. (A) The septal activation is earliest at a posteroinferior site and propagates to the atrioventricular node in a midseptal route. (B) The septal activation propagates primarily through the thick anterior limbic bundles of the atrial septum. See text for further details. Abbreviations are the same as in Figure 3.

rior portion of the sinus wave front reached the anterior surface of the superior vena cava at 15 ms. It then propagated across Bachmann's bundle to the left atrial appendage, depolarizing the anterior surface of the left atrial appendage by 104 ms. The wave front appeared on the posterior surface of the left atrium 55 ms after activation of the sinus node and then propagated toward the left atrial appendage.

After the removal of the right atrial template, cardiopulmonary bypass was instituted and the right atrium was opened vertically about 5 cm from the base of the appendage. The atrial septal template was positioned on the atrial septum as described. During sinus rhythm (Fig 4B), at a cycle length of 1,064 ms, the earliest activation entered the septum below the superior vena cava in the region of the intercaval band. Activation of the atrial septum was asymmetrical, with the wave front propagating most rapidly along the large anterior limbic bundles and anterior medial portion of the atrial septum. The activation reached the inferior atrial septum below the coronary sinus by 85 ms after initial sinus activation. Again, the anterior portion of the sinus wave front reached the anterior surface of the superior vena cava–right atrial junction at 15 ms and then propagated toward the left atrial appendage as in Figure 4A. Epicardial activation, recorded simultaneously with septal activation, demonstrated a similar activation pattern to that shown in Figure 4A. This pattern of atrial septal activation was recorded in 5 patients.

In addition to the pattern of septal activation demonstrated in Figure 4B, there were two other patterns noted. Two patients exhibited the pattern shown in Figure 5A, in which the normal wave front entered the septum posterior to the fossa ovalis. Two other patients demonstrated the pattern shown in Figure 5B, in which the septal wave front entered superiorly, anterior to the superior vena cava.

Atrial Septal Activation During Atrial Pacing

Figure 6 demonstrates an example of right (see Fig 6A) and left (see Fig 6B) atrial pacing at a cycle length of 400 ms. As shown in Figure 6A, the wave front entered the anterosuperior atrial septum from the right atrial pacing site and propagated posteriorly and inferiorly, activating the entire atrial septum by 90 ms. Figure 6B illustrates the wave front entering the midseptum from the left atrial pacing site. In 3 additional patients, mapping also was done during left atrial pacing. The activation pattern of the atrial septum was similar to that in Figure 6B in each.

Atrial Septal Activation During Ventricular Pacing and Orthodromic Reciprocating Tachycardia

Retrograde atrial septal activation during ventricular pacing was varied. In 1 patient with WPW syndrome due to a posterior septal accessory pathway, retrograde atrial septal activation occurred initially beneath the os of the coronary sinus (Fig 7A), thus indicating that specific location to be the site of atrial insertion of the accessory pathway. However, retrograde activation during reciprocating tachycardia in the same patient occurred earliest posterior to the coronary sinus (Fig 7B). Earliest retro-

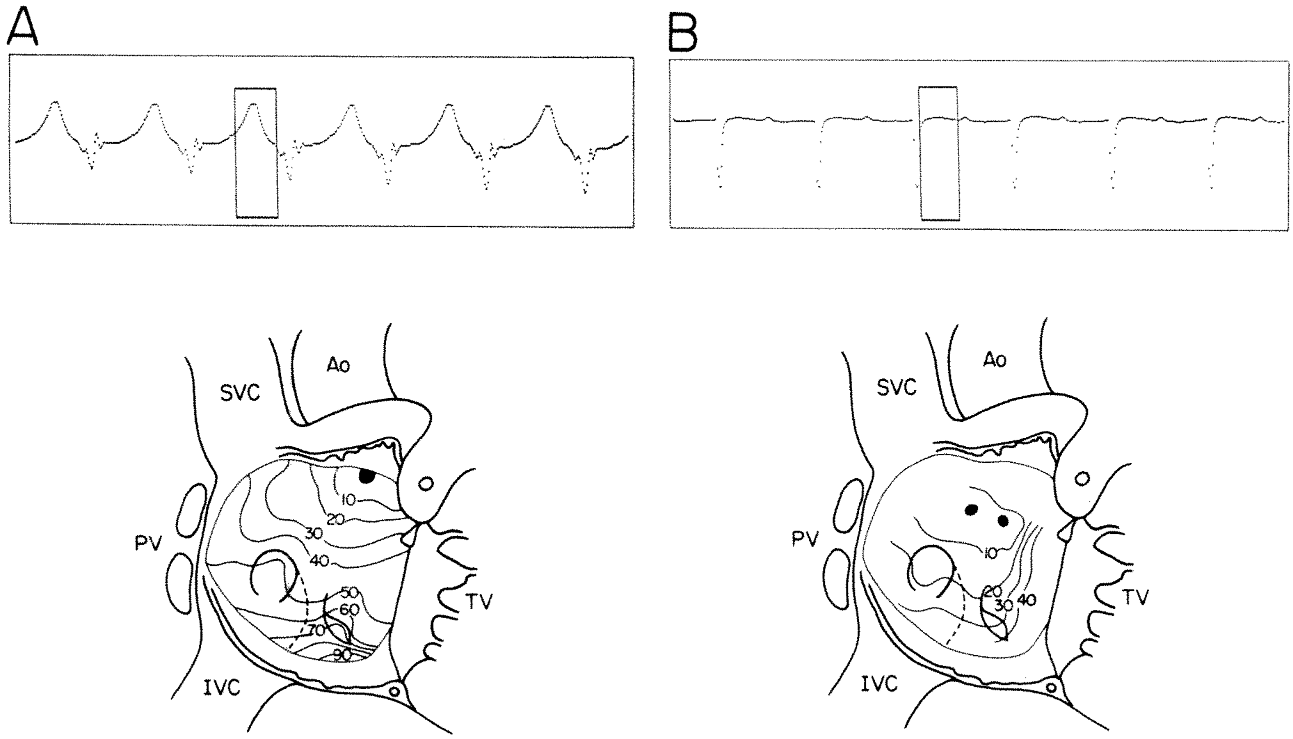

Fig 6. Atrial septal activation maps during (A) right atrial pacing (cycle length = 400 ms) and (B) left atrial pacing (cycle length = 400 ms). See text for further details. Abbreviations are the same as in Figure 3.

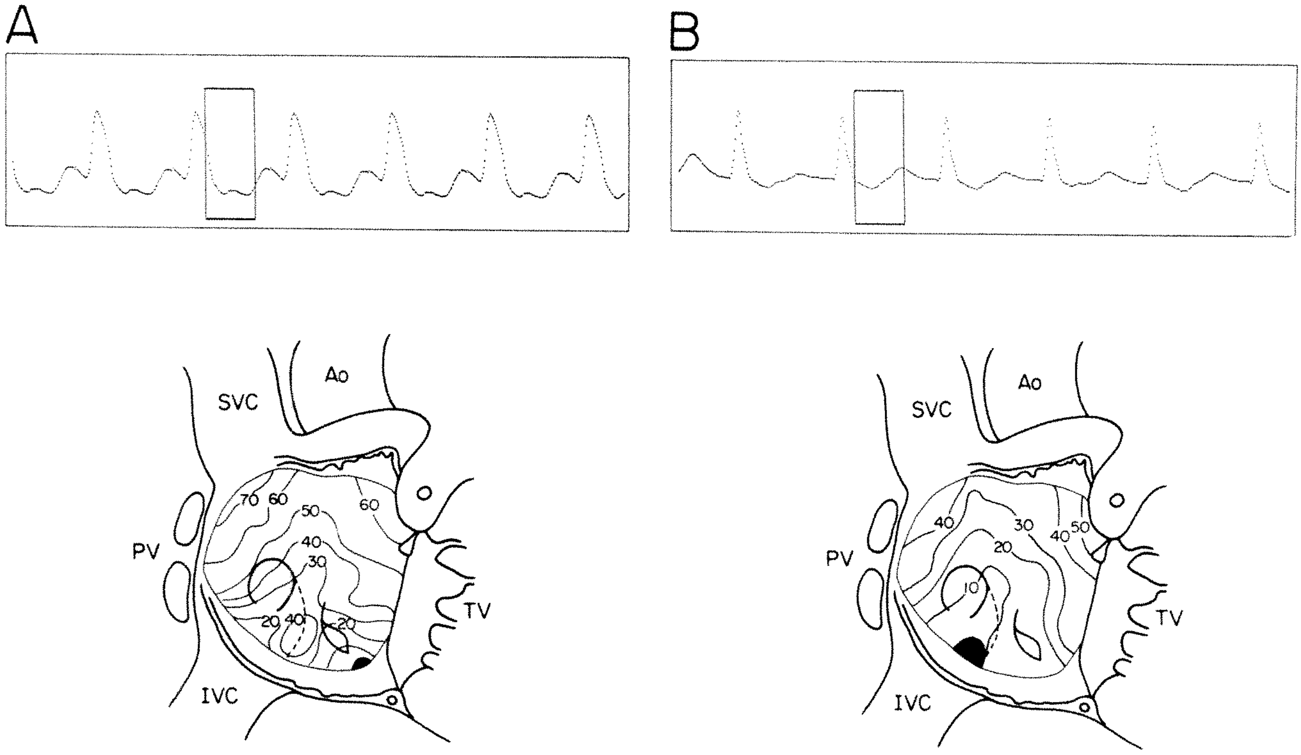

Fig 7. (A) Atrial septal activation during ventricular pacing in a patient with a posterior septal accessory pathway (Wolff-Parkinson-White syndrome). (B) Atrial septal activation in the same patient during orthodromic reciprocating tachycardia. The disparate sites of retrograde atrial septal activation indicate the presence of a wide band of accessory tissues inserting on the atrial septum or multiple atrial insertion sites of a single accessory pathway. Abbreviations are the same as in Figure 3.

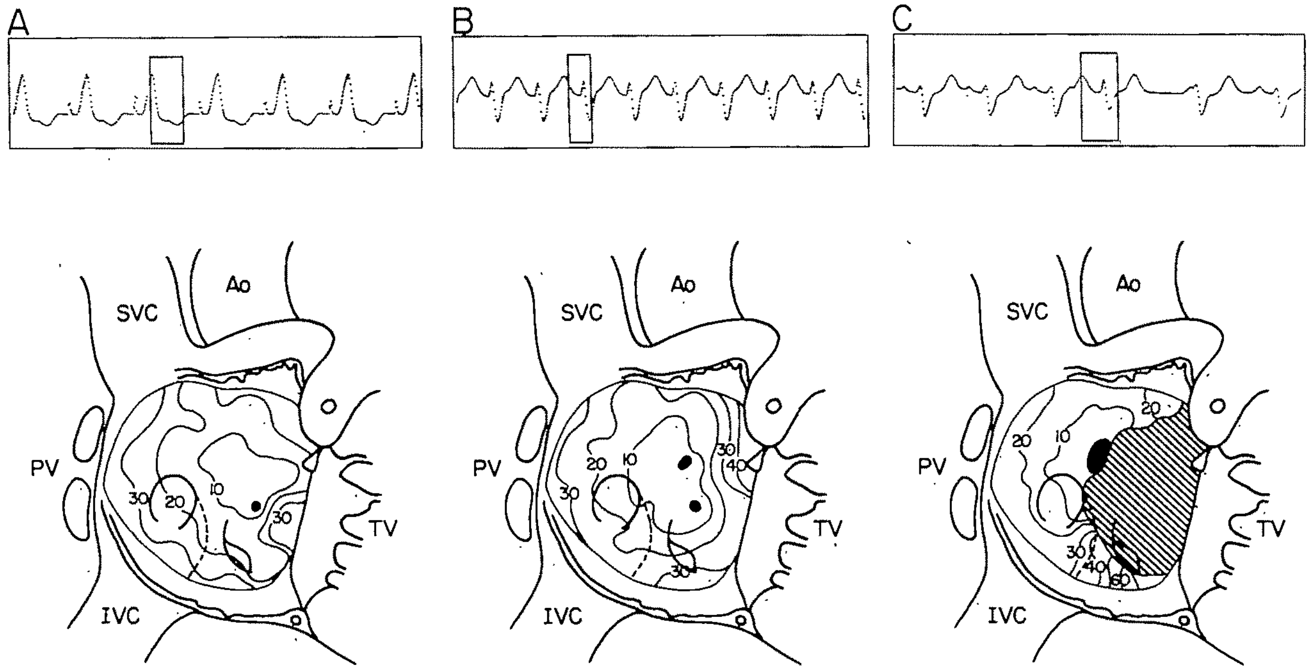

Fig 8. (A) Atrial septal activation during ventricular pacing in a patient with Type A atrioventricular (AV) node reentrant tachycardia. (B) Atrial septal activation in the same patient during AV node reentry tachycardia showing earliest activation (black dots) *anterior and superior to the triangle of Koch. (C) An atrial echocardiographic beat following the application of multiple 3-mm cryolesions to the triangle of Koch. The* shaded area *shows the cryoablated tissue. Abbreviations are the same as in Figure 3.*

grade activation during ventricular pacing in patients with AVNRT occurred in the anterior portion of the triangle of Koch (Figs 8A, 9A) as expected, whether or not the patient had Type A or Type B AVNRT (Figs 8B and 9B, respectively).

Atrial Septal Activation During AV Node Reentry Tachycardia

The atrial septum was mapped during AVNRT in 4 patients. The AVNRT was induced with programmed

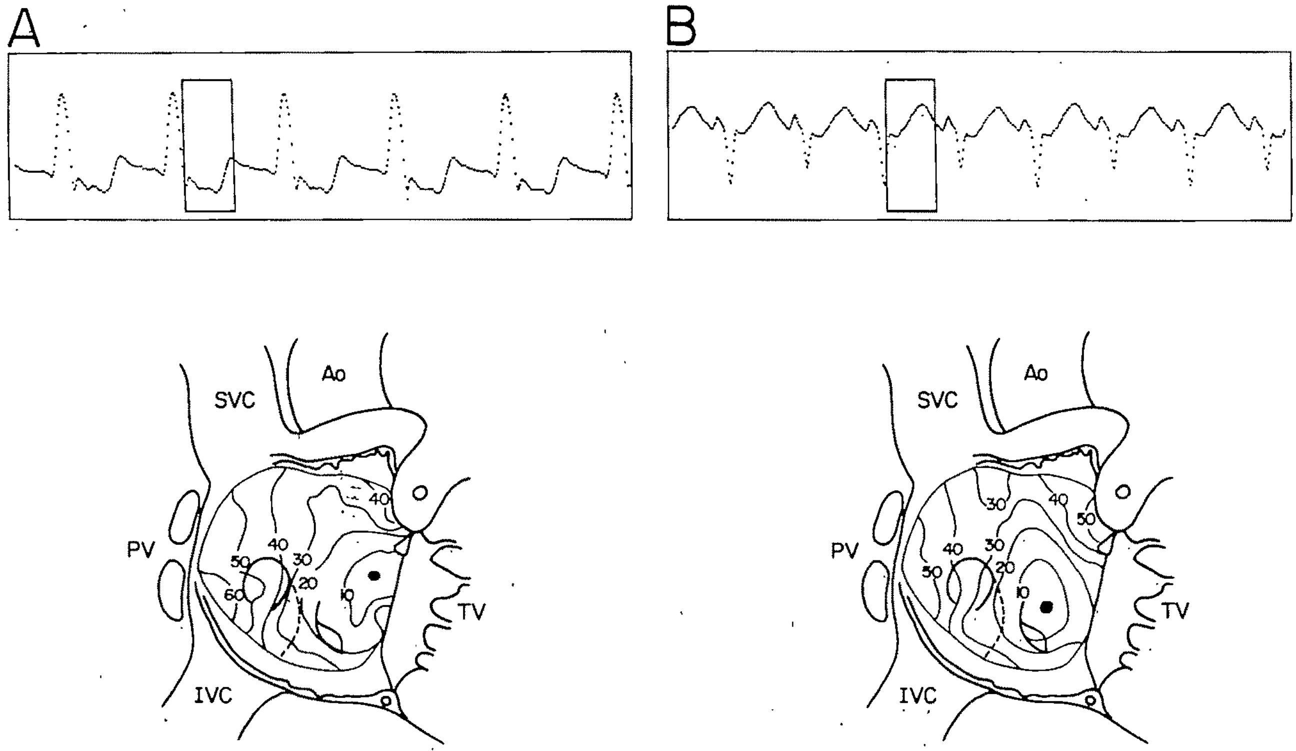

Fig 9. (A) Atrial septal activation during ventricular pacing in a patient with Type B atrioventricular (AV) node reentry tachycardia. (B) Atrial septal activation during AV node reentrant tachycardia in the same patient showing earliest activation (block dots) *posteriorly and within the confines of the triangle of Koch. Abbreviations are the same as in Figure 3.*

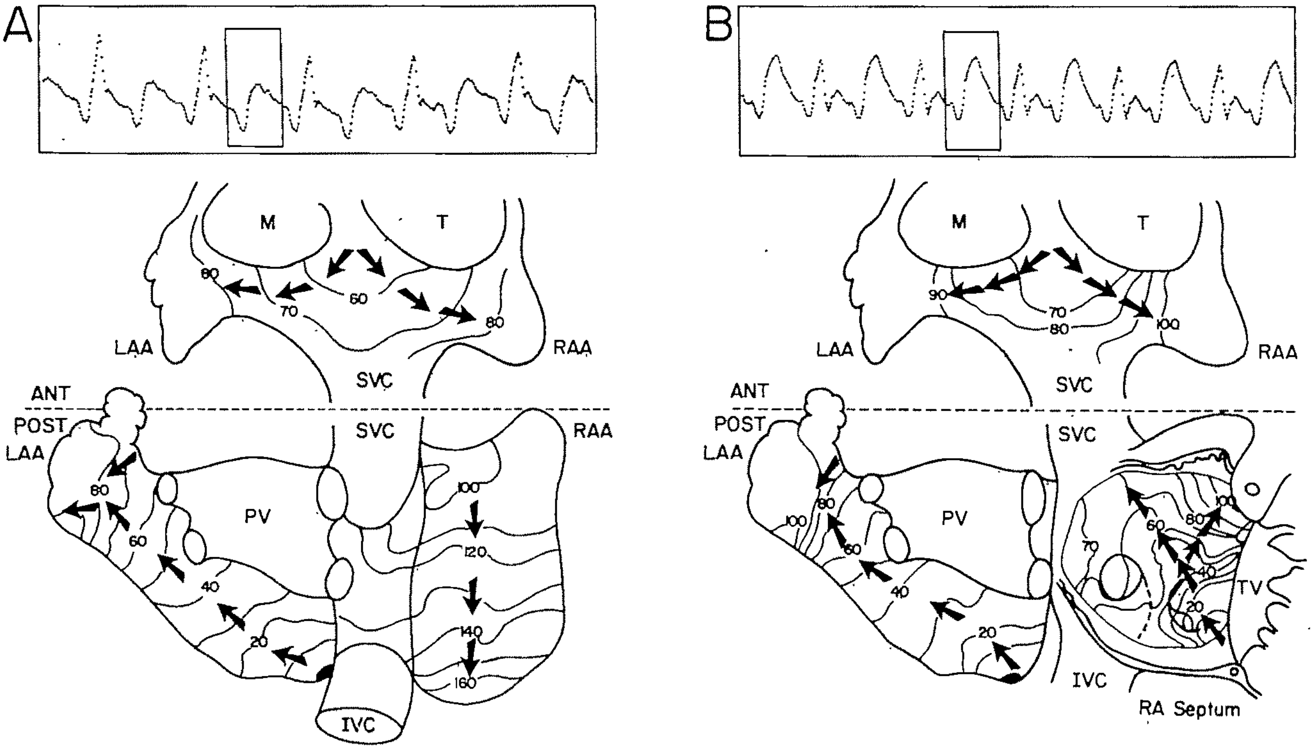

Fig 10. (A) One cycle of atrial epicardial activation during sustained atrial flutter. During the same sustained run of atrial flutter, the atrial septum was mapped (B) along with the posterior left atrium and anterior atria. A complete macroreentrant circuit is suggested by the maps involving propagation from just beneath the os of the coronary sinus (B), upward across the atrial septum to the base of the superior vena cava, and back down the posterior right atrium (A) to return to the region of the coronary sinus os. The left atrium is activated passively by this reentrant circuit involving the right atrium and atrial septum. Abbreviations are the same as in Figures 3 and 4.

stimulation or occurred spontaneously. An example of the retrograde septal activation sequence is illustrated in Figure 8. During AVNRT in this patient, two widely separated areas of the atrial septum were activated almost simultaneously (see Fig 8B). One of these sites was the same as the earliest site recorded during ventricular pacing (see Fig 8A). The second site was located outside the triangle of Koch. Multiple cryolesions were placed within and extending beyond the triangle of Koch (Fig 8C, shaded zone). Although AVNRT was ablated, single atrial echocardiographic beats were still inducible with programmed stimulation. A map of one of the atrial echocardiographic beats demonstrated earliest activation at the edge of the cryoablated septal region (see Fig 8C).

In 2 other patients with AVNRT, the earliest sites of atrial septal activation during AVNRT were anterior to the tendon of Todaro. In another patient, the earliest atrial septal activation site during AVNRT was anterior to the os of the coronary sinus (see Fig 9B). In this patient, the earliest atrial septal activation site during ventricular pacing (cycle length = 450 ms) was the middle portion of the triangle of Koch between the coronary sinus and the membranous AV septum (see Fig 9A).

Atrial Septal Activation During Atrial Flutter

The atrial septum was mapped during atrial flutter in 5 patients. Figure 10A shows an example of epicardial activation during atrial flutter at a cycle length of 238 ms. The activation of the posterior left atrium propagated toward the left atrial appendage. Fifty-two milliseconds later, the activation wave front emerged from the anterior atrial epicardium at the junction of the atrial septum and spread out toward both the right and the left atrial appendages. This wave front reached the posterosuperior right atrium at 90 ms and spread toward the inferior aspect of the right atrium. In the same patient, the atrial septum was mapped along with the anterior atria and the posterior left atrium. The atrial flutter was sustained, but the cycle length had decreased slightly to 225 ms.

Figure 10B demonstrates an activation map of the atrial septum during this arrhythmia. Three milliseconds after activation of the left posterior atrial epicardium, the septum inferior and anterior to the coronary sinus was activated, and the wave front spread across the septum. At the same time, the activation spread across the posterior left atrium toward the left atrial appendage as shown in Figure 10A. The activation wave emerged at the anterior portion of the atrial epicardium near the atrial septum at 65 ms and then spread toward both the left and the right atrial appendages, similar to the previously recorded epicardial map (see Fig 10A).

During mapping of the atrial septum, two types of atrial flutter were observed. In one type, the activation propagated in the atrial septum in the inferior to superior direction (n = 2) (see Fig 10A) and in the other type, it propagated across the atrial septum in the superior to inferior direction (n = 3).

Comment

Electrical propagation in the atrial septum has been studied in animals [2–4, 6] and in humans [7–10]. The atrial septum is important for electrical conduction from the sinus node to the AV node in normal sinus rhythm [1–4], and also may be an important component in many cardiac arrhythmias. Techniques for recording electrograms from the septum using a hand-held electrode or an endocardial catheter [7–11] are limited by the number of simultaneous recording sites, by the time limitations of cardiopulmonary bypass, and by the lack of anatomical correlation between patients. In the present study, the entire atrial septum and atrial epicardium were studied during various normal and abnormal rhythms. Mapping during these rhythms is important not only for understanding the mechanism of atrial arrhythmias, but also in guiding surgical management.

Various techniques [6, 13, 14, 17–19] have been used to map the epicardial or endocardial activation sequence. The use of an electrode template that conforms to atrial anatomical landmarks with a constant interelectrode distance provides a means of attaining reproducible positioning of the electrode in relation to the anatomy [14, 17]. Furthermore, placement of the electrode template before mapping allows the recording of activation sequences without cardiac manipulation. In the first 4 patients, a flat, round Silastic template containing 48 bipolar electrodes was used. However, there were several problems with that template. The atrial septum is not a flat surface. Anatomically, viewed through a right atriotomy, the atrial septum is thicker in the anterior limbus of the fossa ovalis and in the eustachian ridge, and there are depressions over the fossa ovalis and the coronary sinus. During mapping of the atrial septum, blood draining from the coronary sinus hindered good contact of the template with the atrial septum. In addition, the flat septal template did not permit reproducible positioning of the electrodes relative to specific anatomical landmarks.

Because of these problems, a template was fashioned from a plaster cast of the human right atrium. A hole was made in the template for insertion of a suction tip into the coronary sinus for aspiration of coronary sinus blood and to provide fixation of the template at a constant anatomical landmark. High-quality analog electrograms and excellent anatomical reproducibility were obtained within individual patients as well as between patients.

The atrial activation sequence in the atrium was described in animal and human hearts as early as the beginning of the 20th century [20]. The pattern of spread over the atrial septum was noted to be radial in the broad sense. In the present study, the isochronous atrial septal maps demonstrated areas of rapid propagation and slow propagation of excitation. During sinus rhythm, the spread of activation in the atrial septum was faster in the anterior limbic area and anterior part of the atrial septum than across the fossa ovalis. The activation patterns were similar to those seen in animal studies with activation spreading preferentially along the thicker muscle bundles [2–4, 21].

Atrial activation sequences during supraventricular tachycardia, atrial flutter, and atrial fibrillation have been studied to a limited extent in animals [6, 19, 22–24] and in patients during preoperative and intraoperative electrophysiological studies [7, 8, 12–14, 25]. In the present study, the computerized mapping system and multielectrode template permitted various supraventricular arrhythmias to be studied in detail intraoperatively.

In 1 patient with WPW syndrome due to a posterior septal pathway, the site of earliest activation recorded during ventricular pacing was different from that during orthodromic reciprocating tachycardia. Preoperative and intraoperative mapping studies with epicardial electrodes had suggested a single bypass tract in the left posterior septal region. During ventricular pacing, the earliest site of activation was the extreme anteroinferior aspect below the os of the coronary sinus, but during orthodromic reciprocating tachycardia, the region posterior to the coronary sinus was activated 16 ms earlier than the earliest site during ventricular pacing. This observation suggested that the accessory pathway might be a broad band of fibers that conducted preferentially across one end of the band or, alternatively, that two close accessory pathways or branching accessory pathways [25] were present in the same region. We [26] previously described this concept theoretically, and Jackman and co-workers [25, 27] documented it electrophysiologically. This represents an example of the limitation of epicardial mapping alone for localizing a septal accessory pathway in patients with WPW syndrome [28]. In this patient, complete dissection of the entire posterior septal space was performed, and the postoperative study confirmed successful surgical division of the accessory pathway. This case confirms the importance of a complete, broad dissection technique for patients with WPW syndrome [26], and illustrates the usefulness of mapping the atrial septum in patients with septal bypass tracts.

During AVNRT, the earliest sites of activation were outside the boundary of the triangle of Koch. In 3 patients, the earliest site of activation during AVNRT was anterior and superior to the tendon of Todaro and in 1 patient, the earliest site of activation was near the os of the coronary sinus (see Figs 8, 9). Ross and associates [9] mapped atrial septal activation with fine-needle electrodes during AVNRT to locate the earliest site of atrial activation. Their data also demonstrated early activation superior or inferior to the AV node during AVNRT.

In the present study, the septal activation sequence during AVNRT was compared with that during ventricular pacing in 3 patients. During AVNRT, the earliest site of atrial septal activation was superior to the tendon of Todaro in 2 patients and anterior to the os of the coronary sinus in the other. However, the earliest site of atrial septal activation was within the triangle of Koch in the region of the AV node during ventricular pacing. This observation implicates the importance of the atrial tissue lying outside the confines of the anatomical AV node as an important component of the reentry circuit in AVNRT. If the proximal common pathway were located within the

AV node itself [29, 30], one would expect the earliest activation site during AVNRT to be at the same site during ventricular pacing and that site to be in the triangle of Koch. Furthermore, these data explain why meticulous surgical dissection or small cryolesions properly placed around the AV node are successful in ablating AVNRT without altering AV node function]9, 31].

The limitations of inducing atrial flutter in animal models similar to that seen in humans, sustaining a stable atrial flutter, and mapping the entire atria make it difficult to elucidate the mechanism of atrial flutter [19, 23, 24]. The data from 2 patients with atrial flutter, data recorded on both the atrial epicardium and the atrial septum, suggest the possible role of the atrial septum as one limb of a macroreentrant circuit and suggest that this arrhythmia may be amenable to control by surgical techniques. The importance of the atrial septum as a part of the reentry limb during atrial flutter was suggested earlier by endocardial catheter mapping studies [7, 8]. However, catheter mapping during flutter in humans is limited by the number of simultaneous recording sites that can be obtained [11] and by the difficulty of correlating the anatomy with the electrophysiological data.

In the present study, after mapping of the left and right atrial epicardium, the right atrium was incised vertically to permit mapping of the atrial septum. The right atrial incision could have changed the activation sequence of atrial flutter, but the cycle length of the atrial flutter after atriotomy was within 13 ms of the cycle length of the flutter mapped epicardially before the atriotomy. Furthermore, the activation sequence in the left atrium and the anterior atrial epicardium during septal mapping after the atriotomy was the same as that during epicardial mapping before the atriotomy. These findings suggest that the atrial flutter activation patterns during septal mapping were the same as those during the epicardial mapping. Mapping of the entire human atrium, including the septum, simultaneously during atrial flutter has not yet been achieved. However, an endocavitary mapping electrode and a computer-assisted mapping system may be important keys to defining the patterns of activation and eventually may lead to a clear understanding of the mechanism of supraventricular arrhythmias. In 3 of the patients with atrial flutter, the tachycardia was terminated abruptly with cessation of atrial pacing, thus further suggesting a reentrant mechanism as the basic mechanism of this arrhythmia.

In summary, the propagation of electrical activity in the atrial septum during normal sinus rhythm, atrial and ventricular pacing, and various supraventricular arrhythmias was studied with a computerized multipoint mapping system. Mapping of the atrial septum during sinus rhythm, atrial pacing, and ventricular pacing demonstrated that the entire atrial myocardium acts as a conducting system, and changes of initiation of activation altered the shapes of activation sequences. Direct mapping of the atrial septum for septal accessory pathways in patients with WPW syndrome enables more accurate localization of those pathways. During AVNRT, the activation data suggest that atrial tissue lying outside the anatomical AV node is a critical link in the reentrant pathway in this common arrhythmia. The maps recorded during atrial flutter implicate the atrial septum as one limb of a macroreentrant circuit and suggest that this arrhythmia may be amenable to control by surgical techniques.

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DISCUSSION

DR COX: I suspect that most of the members in the audience recognize the amount of work that went into this study and that most of it was done by Dr Chang. The direct result of his work of a couple of years ago, in fact, is that we now have the ability to treat some of these patients with atrial flutter and atrial fibrillation by surgical techniques. Thus, his conclusion is proving to be a valid one.

A final comment is that I think this is a good example of what the Graham Traveling Fellowship and other like fellowships can mean to someone who might otherwise not have the option of being involved in studies like these.

Cancer Recurrence After Resection: T1 N0 Non–Small Cell Lung Cancer

Paul Thomas, MD, Lawrence Rubinstein, PhD, and the Lung Cancer Study Group*

The Lung Cancer Study Group entered 907 eligible patients with T1 N0 non–small cell lung cancer in one of three successive clinical trials. At the time of analysis, 201 of these patients were free from malignancy 60 months after operation. Thirty percent of patients who died were free from malignancy at death. Death rates were comparable for the total group (907 patients) and the patients free from malignancy at 60 months (201 patients) (0.086 versus 0.079, respectively); therefore death was not a suitable therapeutic end point. Cancer recurrences were more frequent in patients with nonsquamous carcinoma than those with squamous carcinoma (0.088 versus 0.042); however, this difference was not observed after a 60-month malignancy-free interval (0.035 versus 0.022, respectively). Select comparisons between the total group of 907 patients and the 201 patients free from malignancy at 60 months are noteworthy: (1) the rate of occurrence of new, nonpulmonary malignancies was constant (0.016 versus 0.018, respectively); (2) the rate of pulmonary recurrences decreased (0.043 versus 0.013, respectively); and (3) the rate of occurrence of new lung cancer increased (0.009 versus 0.016, respectively). Therefore, although cancer recurrences decreased with survival, new lung cancer occurrences increased, and the probability of malignant disease appearing more than 60 months after operation for T1 N0 non–small cell lung cancer dictates continued patient surveillance.

(Ann Thorac Surg 1990;49:242–7)

The prognosis for surgically treated patients with T1 N0 M0 non–small cell lung cancer is quite good. The Lung Cancer Study Group (LCSG) [1] reported a recurrence rate of 0.042 and 0.106 per eligible patient per year for patients with squamous cancer and patients with nonsquamous, non–small cell cancer, respectively. Conventionally the success or failure of therapeutic interventions in patients with cancer has been estimated in recurrence-free intervals, time of survival, or both, often with emphasis on the initial 5 years subsequent to intervention. However, these end-point observations may be misleading in groups of patients with low recurrence rates. Therapeutic control of the malignancy is underestimated by overall mortality rates if a significant proportion of the patients die of unrelated causes. On the other hand, treatment success can be overestimated by recurrence rates restricted to the initial 5 years if the risk of a new malignancy developing 5 years or more later is substantial.

In reported series of patients with surgically and pathologically staged T1 N0 non–small cell lung cancer, the numbers of patients are insufficient and the follow-up is too abbreviated to support conclusive statements. The LCSG cooperating institutions are currently following a representative sample of patients with surgically and pathologically confirmed T1 N0 non–small cell lung cancer after surgical treatment (Appendix 1). They have been observed for cancer recurrence, cancer-related death, appearance of new malignancy, and noncancer-related death. The purpose of this report is to summarize the observations to date.

Material and Methods

Eligibility and Study Population

Between July 1977 and November 1988, 907 eligible patients with T1 N0 non–small cell lung cancer were entered in one of three LCSG studies. All patients had complete surgical removal of the lung cancer. Without exception, lymph nodes were removed from the lung hilum and from subcarinal and paratracheal sites for histological examination, a rigorous requirement for accrual to LCSG clinical trials [2]. Patients with prior lung, breast, or renal carcinoma were excluded. In addition, patients previously treated for other malignancies were ineligible unless they had been free from disease 5 years or longer. Informed consent was obtained from each patient.

Patients included were aggregated from the following clinical trial groups: (1) an adjuvant BCG (bacille Calmette-Guérin) immunotherapy trial (LCSG-771); (2) a nat-

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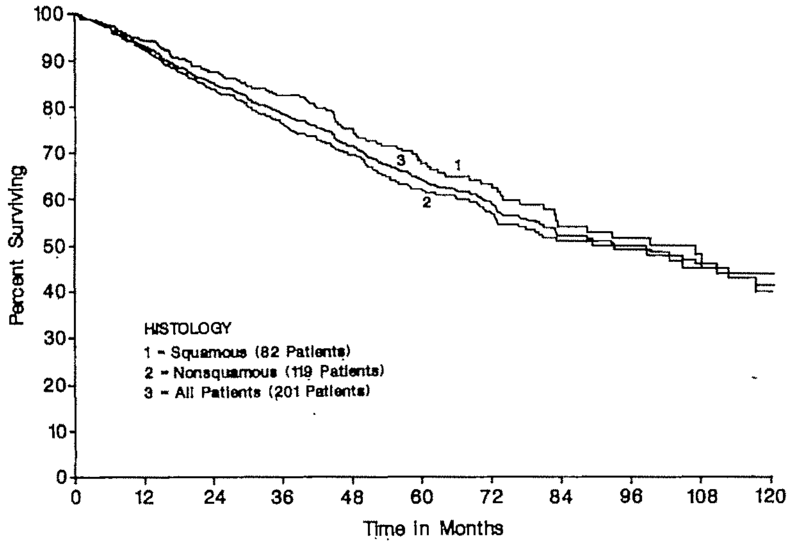


Fig 1. Time to death from all causes after surgical treatment.

ural history catalogue of T1 N0 patients (LCSG-NHC 1); and (3) a limited resection trial (LCSG-821). Adjuvant immunotherapy was not beneficial, and no differences were observed comparing treated and untreated patients [1, 3]. The assumption that the patients from each of the sequential groups represent the same subgroup population of lung cancer patients was validated statistically. There were no differences in selection, time to recurrence, or time of survival in the respective groups of patients. Extensive cross-tabulations and analysis of cell type distributions and randomizations did not reveal any differences between source populations of these patients.

Pathology

The initial pathological interpretations were made by pathologists of the LCSG cooperating institutions, and were reviewed by pathologists at the LCSG pathology reference center to assure uniformity. Electron microscopy was used as necessary to discriminate cell type. The classification of nonsquamous non–small cell carcinoma included adenocarcinoma, bronchoalveolar carcinoma, and large cell carcinoma. Patients determined to be ineligible for histopathological reasons or because of staging error were excluded from analysis.

A diagnosis of cancer recurrence, either regional or distant, was determined clinically and was supported by radiographic evidence of disease or laboratory abnormalities. Tissue confirmation was obtained when clinically feasible or at postmortem examination when possible. Diagnosis of a second primary lung cancer was based on distinguishable histology or, rarely, the presence of a remote lung mass in the absence of other sites of recurrence. Diagnosis of a second primary malignancy in another organ or tissue (eg, colon, bladder, head and neck) was determined by characteristic pathological findings.

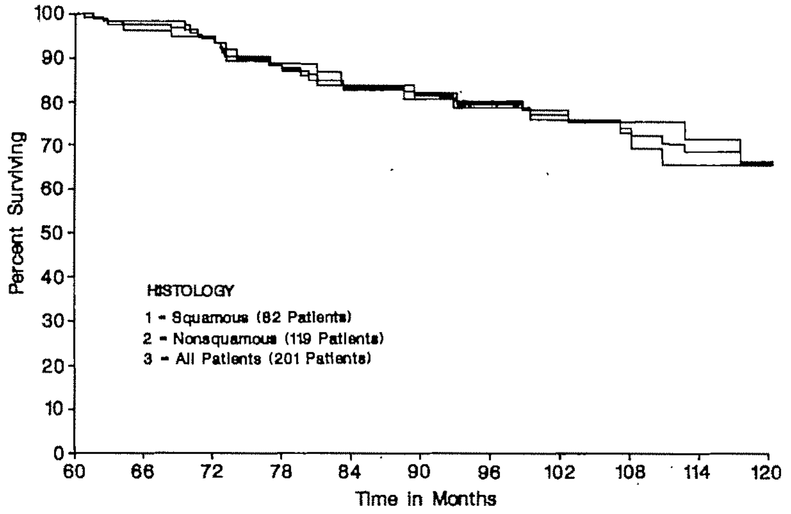


Fig 2. Time to death from all causes among patients free from known malignancy 60 months after surgical treatment.

Table 1. Death Rates[a]

Patient Group	Overall	Squamous	Nonsquamous
All (n = 907)	0.086	0.077	0.092
Disease free at 60 mo (n = 201)	0.079	0.081	0.077

[a] This was calculated as deaths/eligible patient/year.

Table 2. Recurrence Rates[a]

	Histopathology		
Patient Group	Squamous	Nonsquamous	Total
All (n = 907)	0.042	0.088	0.070
Disease free at 60 mo (n = 201)	0.022	0.035	0.030

[a] This was calculated as recurrences/eligible patient/year.

Statistical Methods

Survival times and disease-free intervals were calculated from the postoperative date of randomization or from the date of registration. Recurrence and death hazard rates were estimated by dividing the number of events by person-years of exposure. Nonparametric estimates of survival and recurrence-free survival were obtained by the method of Kaplan and Meier [4]. The prognostic importance of histopathology was assessed by the Cox proportional hazards model [5].

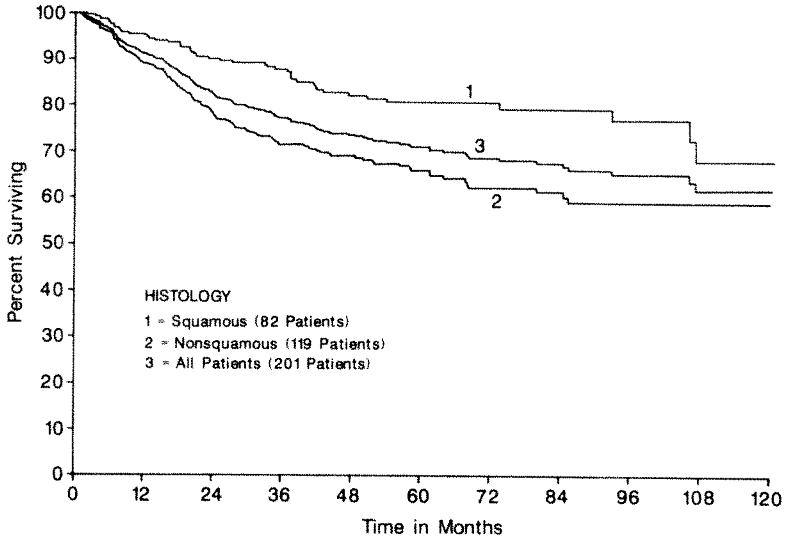
Results

The LCSG participants entered 907 eligible patients with confirmed T1 N0 non–small cell lung cancer into one of the three clinical trials already mentioned. Although the trials were conducted sequentially, the same rigorous criteria for staging and pathological interpretation were applied. The assumption that the patients entered into the immunotherapy trial, the natural history catalogue, and the limited resection trial were representative of the same population of T1 N0 non–small cell lung cancer patients was carefully examined. Comparisons of age, frequency of distribution of histopathological types, preoperative weight loss, and postoperative complications revealed no significant differences [1]. Patients entered in the immunotherapy trial and the limited resection trial were randomly assigned to control and experimental arms that demonstrated no difference in outcome, either beneficial or detrimental. Therefore, patients from these three groups were aggregated for this analysis. At the time of this summary, 201 patients had lived 5 years or longer after surgical treatment and were free from any known malignancy.

The median survival for the 907 patients was approximately 8 years. Survival was not histopathologically dependent (to the extent of being significant) for either the total group of patients (Fig 1) or for the patients who were free from malignancy 60 months postoperatively (Fig 2). Similarly, death rates were not remarkably different (Table 1). Thirty percent of the patients who died were free from any known malignancy at the time of death.

The median time to recurrence of malignancy, including the appearance of a new primary malignancy, was approximately 7.5 years. Nonpulmonary second malignancies developed in 47 patients (5.2%). The distribution of these second malignancies was as follows: breast, 7 patients; colon, 7; prostate, 6; head and neck, 5; bladder, 3; skin, 3; liver, 2; ovary, 2; stomach, 2; rectum, 1 patient; cervix, 1; chest wall, 1; trachea, 1; leukemia, 1; lymphoma, 1; myeloma, 1; and unknown, 3. The first sites of extrapulmonary recurrences followed a distribution pattern previously reported: brain, 35 patients; bone, 24; mediastinum, 18; lymph nodes, 15; liver, 13; pleura, 5; skin, 2; and other, 23. These recurrences are not mutually exclusive; first recurrence was reported for more than one location simultaneously in some instances.

Fig 3. Time to first recurrence (excluding second primary) after surgical treatment.



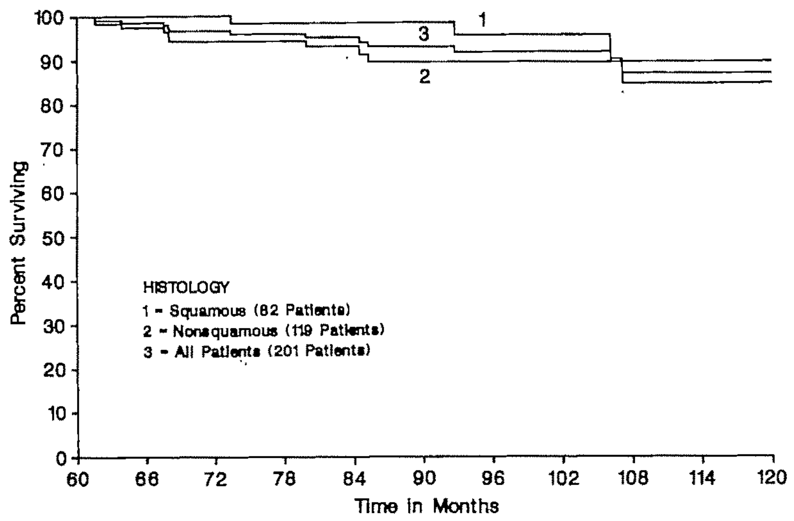


Fig 4. Time to first recurrence (excluding second primary) among patients free from known malignancy 60 months after surgical treatment.

Recurrences were observed more frequently in the first 60 months after operation in patients with nonsquamous carcinoma compared with those with squamous cancer (Table 2; Fig 3). This histopathological difference in recurrence rate was obliterated in patients free from malignancy 60 months after surgical treatment (Fig 4; see Table 2). Also, the overall recurrence rate was lower among patients disease free for 5 years or more postoperatively. In contrast to this decreased recurrence rate after 60 months the occurrence rate for new, nonpulmonary malignancies was unchanged, but the occurrence rate for new pulmonary cancers increased (Table 3; Fig 5).

Comment

The quality and uniformity of the surgical and pathological staging of lung cancer patients practiced by LCSG participants and confirmed by pathological review have been previously reported [6]. This group of 907 patients with T1 N0 non–small cell lung cancer pooled from three sequential LCSG clinical trials is the largest group of such patients prospectively observed after surgical treatment.

Patient survival was not a sensitive estimate of therapeutic effectiveness in this group of patients. The causes of death were frequently not related to malignancy, and the death rate was low. Therefore, death is not a satisfactory end point.

Cancer recurrence, either local or distant, represents treatment failure. The development of a second lung cancer is indicative of persistent or uncontrolled exposure to etiological risk factors. Using restrictive histological criteria for the diagnosis of new primary lung cancer results in an underestimate of true incidence and an overestimate of lung recurrences. However, even with this reservation, it is evident from the data presented that the incidence of recurrence decreases with time and the incidence of new lung cancer increases with time after successful removal of a T1 N0 non–small cell malignancy from the lung. It is probable that at the point of crossover from a dominant risk of recurrence to a dominant risk of new lung cancer, the overall prognosis for patients is not altered. However, application of preventive intervention, if beneficial, would have an important role in the postsurgical management of these patients.

Table 3. Occurrence Rates for Recurrences and New Malignancies[a]

	Recurrences		New Malignancies	
Patient Group	Pulmonary	Extrapulmonary	Pulmonary	Nonpulmonary
All (n = 907)	0.027	0.043	0.009	0.016
Disease free at 60 mo (n = 201)	0.017	0.013	0.016	0.018

[a] Occurrence rates were calculated as occurrences/eligible patient/year.

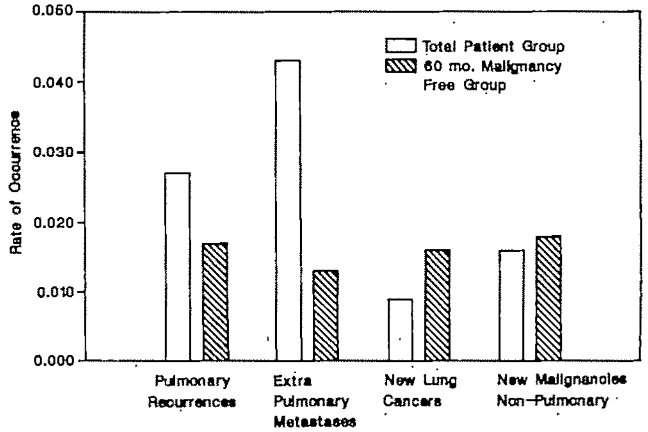


Fig 5. Comparison of rate of first occurrence or recurrence of malignancy between the total group of patients and patients free from malignancy 60 months after surgical treatment.

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Appendix 1. Members of the Lung Cancer Study Group Participating in This Study

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DISCUSSION

DR THOMAS W. SHIELDS (Chicago, IL): Over the years the Lung Cancer Study Group has contributed much to our understanding of the natural history of resected lung cancer. This report by Thomas and associates is no exception. They have made a number of major observations.

A significant percentage of patients with T1 N0 disease who die within the follow-up period will do so of causes other than their initial tumor, which was 30% in this study. In our Veterans Administration studies, it was a little bit less, approximately 23%.

Tumor recurrence is more common and earlier in the nonsquamous lesions, but with the passage of time, in both the squamous and nonsquamous groups, the survival tended to merge. It reached this point at about 5 years, there being no significant difference between the survival of the two groups at this point.

Also with the passage of time, the incidence of secondary primary lung tumors becomes greater than the incidence of recurrence of the original disease. There is also a frequent occurrence, approximately 5%, of a second primary tumor in another organ system. Therefore, this means that constant and frequent postoperative surveillance is mandatory in these patients throughout their life span.

I would suggest that these patients be seen at least three if not four times a year, at which time a history, physical and chest radiographs (posteroanterior and lateral views), as well as sputum cytology should be done. I think it is important to emphasize that the chest roentgenogram should always be compared not to the most recent but to the oldest one done in the distant past, as comparing the new film to the most recent, you may well miss early subtle changes.

Because of the high rate of survival after resection of T1 N0 lesions and the aforementioned increasing incidence of a second primary lung tumor, it is imperative that the most conservative but adequate resection be carried out in these patients. Although the Lung Cancer Study Group has not yet formally reported their prospective randomized trial of lobectomy versus a lesser section for T1 N0 lesions, one may assume from their inclusion of the data from these patients in this study today that a lesser resection may possibly be as efficacious as a lobectomy. If so, this would certainly support the contention made by Read and co-workers in their report [1].

Therefore, from this assumption and from the report by Read and co-workers, I think that we must realize that a segmentectomy, when properly applied—and that is the important thing, when it is properly applied—should be a standard option in patients with peripheral lung cancer regardless of their pulmonary function.

Finally, along these lines of lesser resection, I would like to ask Dr Thomas, if he feels free to discuss it, what about the randomized trial of lesser resection versus lobectomy? How did it work out? I know that it is not completely evaluated, but as you did include the data from this study in your report, there must be some information you could give us.

DR RICHARD K. HUGHES (Los Angeles, CA): I have a hard time accepting the idea of recurrence after 3 years, and especially after 5 years in T1 N0 lesions. How did you tell the difference between a recurrence or a new primary lesion in these late so-called recurrences? Did there always have to be different cell types?

DR THOMAS: With regard to the limited resection, I am sorry to say that I am not going to tell you the answer. Bob Ginsberg will tell us when that study is mature enough for meaningful data. The informal, unofficial comment is that up to a recent look at that study there was no difference in recurrences.

Dr Hughes, we used a very strict definition of recurrence. There was no question about the late distant metastatic recurrences being from a primary T1 N0 lung cancer. There is no question about those patients who had more than one metastatic lesion or had disease of the mediastinum as having late recurrence. I agree with you that there is probably a serious underestimate of the true number of patients with new pulmonary cancer. However, we do not have a good way to discriminate between recurrence and new primary cancer, and I accept your suggestion that we missed a fair number.

One final comment. Certainly this would be an ideal group of patients to put under surveillance when and if we have some sort of preventive intervention to demonstrate efficacy.

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Diaphragmatic Plication for Unilateral Diaphragmatic Paralysis: A 10-Year Experience

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Unilateral paralysis of the diaphragm due to nonmalignant disease is an uncommon disorder previously thought to have benign implications. Some patients, however, experience dyspnea and orthopnea with impairment of pulmonary function. Unilateral diaphragmatic plication was performed on 17 patients (16 men and 1 woman with a mean age of 53.7 years [range, 28 to 74 years]) during the last 10 years. Preoperatively each patient was shown to have paradoxical movement of the paralyzed diaphragm on sniffing and to have a reduction in forced vital capacity and lung volumes. These reductions were greater when the patient was in the supine position. All patients had moderate hypoxemia (mean arterial oxygen tension, 73.1 ± 10.9 mm Hg). Plication was performed by imbricating the diaphragm in layers through a thoracotomy incision. After plication, all patients showed both subjective and objective improvement. Six patients were reassessed 5 or more years after plication (range, 5 to 7 years), and the improvement was maintained. Diaphragmatic plication is a safe and effective procedure for adult patients with dyspnea due to unilateral diaphragmatic paralysis; furthermore, the initial improvement is maintained.

(Ann Thorac Surg 1990;49:248–52)

Unilateral paralysis of the diaphragm not due to malignant disease is an uncommon condition. When it does occur, it is generally thought to contribute little toward the development of symptoms. However, there is a well-defined group of patients in whom paralysis of the diaphragm causes troublesome dyspnea. Our group [1] previously reported major symptomatic improvement following diaphragmatic plication in a small group of select patients and demonstrated significant improvement in objective measures of respiratory function. The procedure carried little attendant morbidity and no mortality.

Over the last 10 years, 17 patients have undergone diaphragmatic plication. This report details our overall experience and includes the assessment of those patients followed for more than 5 years.

Material and Methods

Between January 1979 and June 1989, 17 patients underwent unilateral plication of the diaphragm. The mean age was 53.7 ± 13.8 years (range, 28 to 74 years). There were 16 men and 1 woman. The left side was affected in 9 patients and the right side in 8. Five of the patients were smokers, and 6 were former smokers; 6 of the patients were nonsmokers.

Several possible causes of diaphragmatic paralysis were identified: trauma (3 patients), cervical spondylosis or postpneumonic condition (2 patients each), and a sequel to either radiotherapy or, possibly, a viral disease (1 patient each). The cause in 8 patients was unknown. Eleven of the 17 patients had a concurrent medical problem: chronic obstructive airway disease in 5, asthma in 3, and Klinefelter's syndrome, ischemic heart disease, and carcinoma of the breast (operation and radiotherapy) in 1 each.

All patients complained of dyspnea on exertion and orthopnea. The mean time from onset of symptoms to operation was 1.8 years (range, 4 months to 4 years). The decision to recommend surgical intervention was made by consensus between the referring respiratory physician and the thoracic surgeon. The essential considerations were that the patient had effort dyspnea that interfered with his or her activities and orthopnea as well as respiratory function test results typical of diaphragmatic paralysis of the diaphragm [1–3].

Patient Assessment

In every instance, the affected hemidiaphragm was raised and moved paradoxically on sniffing. Pulmonary function tests (forced vital capacity, forced expiratory volume in 1 second) were performed and lung volumes (total lung capacity, functional residual capacity, expiratory reserve volume, residual volume) and diffusion coefficient were measured with the patient sitting and supine before and at least 6 weeks after operation. The studies were repeated after 5 years in 6 patients. An equilibration time of ten minutes was allowed in each posture before performance of the tests. Predicted lung volumes and diffusion coefficients were taken from Cotes [4]. Blood gas estimation was performed on samples obtained from radial artery punctures.

Each patient was asked to grade his or her dyspnea on a visual analog scale (graded 0 through 10) before and 6 weeks after operation. Patients were given a piece of

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Table 1. Dyspnea Scores and Physiological Measurements Before and After Unilateral Diaphragmatic Plication[a]

Variable	Before Operation (n = 17)	After Operation (n = 17)	p Value	5- to 10-Year Follow-up Before (n = 6)	5- to 10-Year Follow-up After (n = 6)	p Value
Dyspnea score	7.4 ± 0.8	3.3 ± 0.9	<0.001	5.8 ± 0.7	2.4 ± 0.5	<0.001
FVC						
Sitting	2.7 ± 0.7	3.2 ± 0.5	<0.001	2.9 ± 0.8	3.4 ± 1.0	<0.02
Lying	1.9 ± 0.5	2.7 ± 0.6	<0.001	2.3 ± 0.6	3.1 ± 1.1	<0.05
TLC						
Sitting	4.1 ± 1.6	4.5 ± 1.7	<0.002	4.6 ± 1.0	5.4 ± 0.9	<0.05
Lying	3.4 ± 0.8	4.2 ± 1.7	<0.002	4.2 ± 1.2	5.0 ± 0.9	<0.05
FRC	2.5 ± 0.2	2.9 ± 0.2	<0.01	2.2 ± 0.9	2.9 ± 0.4	NS
ERV	0.6 ± 0.2	0.9 ± 0.2	<0.01	1.1 ± 0.9	1.2 ± 0.3	<0.05
RV	1.9 ± 0.2	2.0 ± 0.7	NS	1.7 ± 0.7	1.9 ± 0.2	NS
DLCO (% predicted)	85 ± 4.5	100 ± 6.9	<0.05	87 ± 14.1	98 ± 22.7	<0.05
PaO_2	73.1 ± 10.9	85.6 ± 13.2	<0.001	75.7 ± 14.3	93.4 ± 10.4	<0.01
$PaCO_2$	39.8 ± 6.7	38.4 ± 6.1	NS	31.4 ± 8.6	38.9 ± 3.6	NS

[a] Lung volumes are measured in liters and blood gas estimations in millimeters of mercury.

DLCO = diffusion coefficient; ERV = expiratory reserve volume; FRC = functional residual capacity; FVC = forced vital capacity; NS = not significant; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; RV = residual volume; TLC = total lung capacity.

paper with a scale from 0 through 10 representing degrees of breathlessness from normal to most breathless, and were asked to score the degree of breathlessness they experienced.

Surgical Technique

Diaphragmatic plication was performed through a posterolateral thoracotomy in the seventh intercostal space. The lung and mediastinum were examined to exclude unsuspected pathological processes. The diaphragm was then plicated in successive layers until it became taut. Interrupted nonabsorbable mattress sutures were used and, to prevent tearing out of sutures, the penultimate and final layers were buttressed with Teflon pledgets. An intercostal drain was left in place and was usually removed 24 hours postoperatively.

Statistical Analysis

All results are expressed as the mean ± the standard error of the mean. The paired Student's t test was used to calculate statistical differences. Those with p values less than 0.05 were considered significant.

Results

Before operation, the mean breathlessness score was 7.4 ± 0.8 (0 = no breathlessness, 10 = maximum breathlessness). All patients had moderate hypoxemia (mean arterial oxygen tension, 73.1 ± 10.9 mm Hg). There were reductions of spirometric values and lung volumes, and these effects were exaggerated when the measurements were repeated with the patient in the supine position (Table 1).

After plication, there was significant subjective improvement in breathlessness and orthopnea in all 17 patients. The breathlessness score fell from 7.4 ± 0.8 to 3.3 ± 0.9 ($p < 0.001$). There were significant improvements in spirometric values and lung volumes (total lung capacity, functional residual volume, and expiratory reserve volume). Although there was still a fall in the volumes measured with the patient supine, the effect was less obvious than before operation. There was a small but significant improvement in the transfer factor (diffusion coefficient). Arterial oxygen tension improved from a mean of 73.1 ± 10.9 to 85.6 ± 13.2 mm Hg ($p < 0.001$). There were no significant changes in residual volume and arterial carbon dioxide tension. The results are shown in Table 1.

Postoperative chest radiographs showed that the plicated diaphragm was lowered to an almost normal position (Figs 1, 2).

Six of the 8 patients who had undergone diaphragmatic plication at least 5 years previously were reassessed in the same way. The improvements noted soon after operation were maintained (Fig 3; see Table 1).

There were no serious postoperative complications, and the mean hospital stay was 11 days (range, ten to 15 days).

Comment

Nonmalignant unilateral diaphragmatic paralysis is an uncommon condition. A large number of causes have been described: poliomyelitis, herpes zoster [5, 6], measles, typhoid, diphtheria, chronic neurological conditions, injury to or disease of cervical vertebrae, pulmonary infection, mediastinitis [7], cardiac operation [8, 9], aortic aneurysm [10], and in association with pneumonia [11, 12]. In many cases, diaphragmatic paralysis occurs without satisfactory explanation.

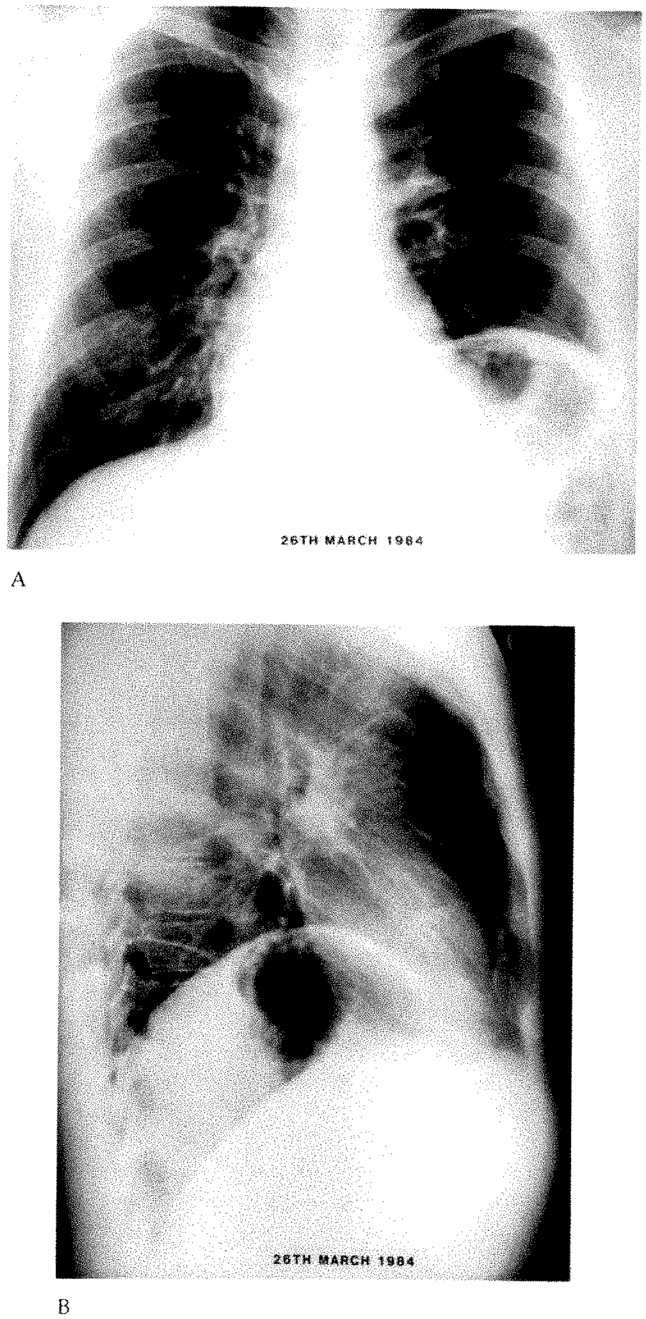

Fig 1. Preoperative (A) posteroanterior and (B) lateral chest radiographs of a 28-year-old man with paralysis of the left hemidiaphragm.

The prognosis for patients with nonneoplastic diaphragmatic paralysis is thought to be good [13–15]. Although patients with the condition may be asymptomatic [14], there is a group of patients who have respiratory symptoms and impairment of pulmonary function [16]. The clinical features include breathlessness on exertion and orthopnea; there may be accompanying gastric symptoms, particularly with left-sided paralysis. The diagnosis is suggested by a raised hemidiaphragm on the chest radiograph, and is confirmed by observing paradoxical movement of the paralyzed diaphragm on sniffing using fluoroscopy.

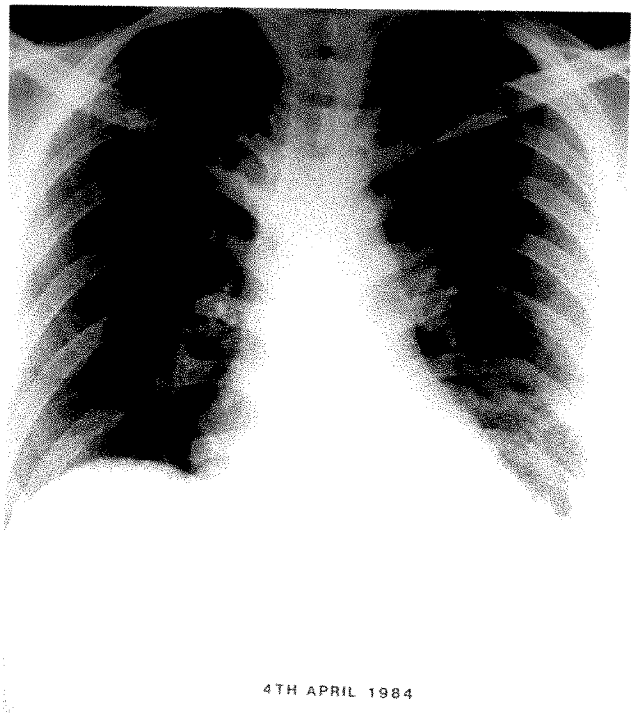

Fig 2. Chest radiograph of the same patient soon after diaphragmatic plication.

The patients in this study showed the typical pulmonary function abnormalities described in unilateral paralysis of the diaphragm [2, 3, 17, 18]. They were observed to have reduction in forced vital capacity, total lung capacity, and functional residual capacity; these reductions were greater when the patients were lying down. The patients also showed hypoxemia with a mean arterial oxygen tension of 73.1 mm Hg. No large series has reported the results of plication to relieve breathlessness, though the operation has been performed previously for a variety of symptoms [19, 20]. Our earlier report in 1985 [1] showed good symptomatic and physiological improvement in 7 patients. That series has now been extended, and the original results are confirmed. Subjectively, all patients were less breathless (at least 5 reported decreased dyspnea in the immediate postoperative period), and objective assessment 6 weeks after operation showed there was significant improvement in spirometric values, static lung volumes, and oxygenation.

It could be argued that over time, the taut, plicated diaphragm would gradually stretch and distend back to its original paralyzed position. However, we have demonstrated that after 5 years or more, the improvement in symptom scores, pulmonary function test results, and position of the diaphragm on the radiograph in the postoperative period is maintained. It appears that diaphragmatic plication is a safe and effective procedure for adult patients with dyspnea due to diaphragmatic paralysis; furthermore, the initial postoperative improvement is maintained over a long period.

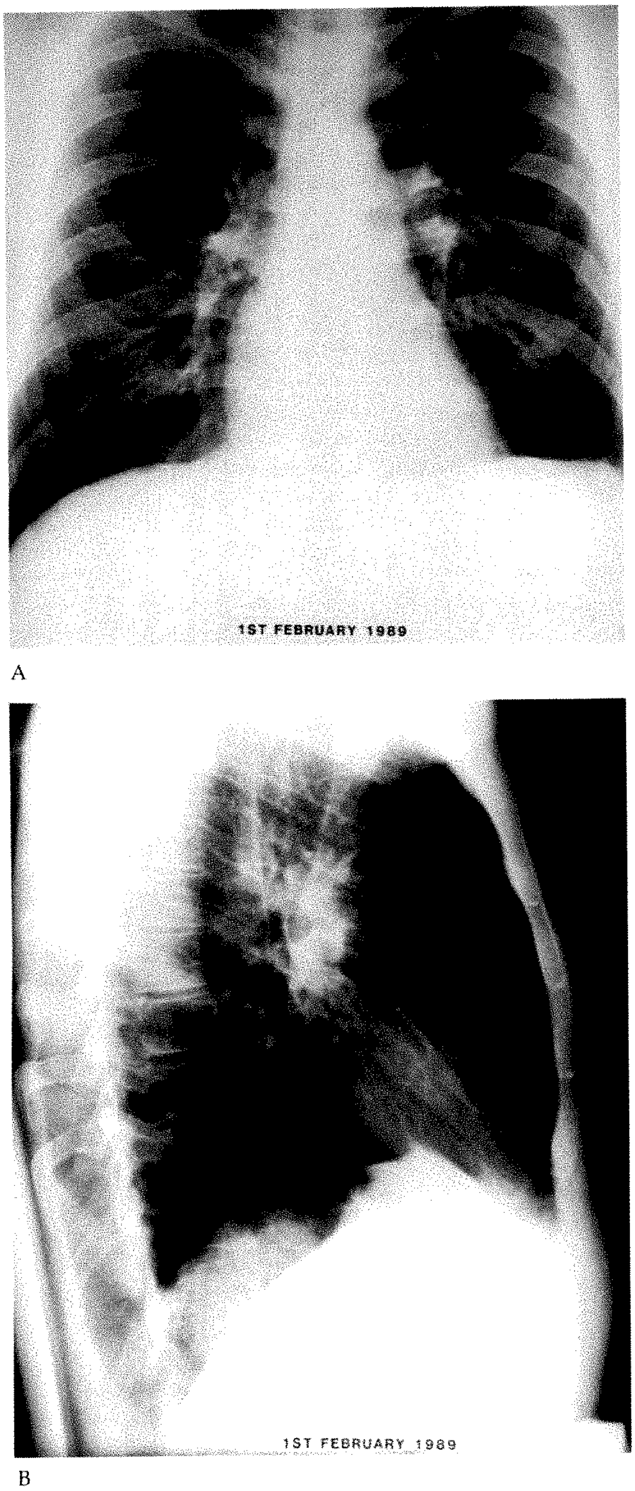

Fig 3. (A) Posteroanterior and (B) lateral chest radiographs of the same patient 5 years after diaphragmatic plication. Note that the position of the plicated diaphragm is maintained.

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DISCUSSION

DR ROBERT M. SADE (Charleston, SC): Diaphragmatic paralysis producing symptoms in adults is an uncommon problem, which probably accounts for the paucity of information available regarding its treatment and long-term outcome. This report by Graham and associates makes an important contribution to our understanding of this entity. Four years ago, their group published data indicating that patients with symptoms due to paralysis of a diaphragm had significant improvement in dyspnea and orthopnea, as well as improvement in objective measures of pulmonary function, after diaphragmatic plication.

With this report, they have extended their observations further and provided us unique data on the intermediate-term outcome of diaphragmatic plication for patients with symptomatic diaphragmatic paralysis. We now know that plication holds up quite well for at least 5 years, with continuing relief of symptoms and continuing improvement in objectively measured pulmonary function, as well as persistence of low position of diaphragm on chest roentgenogram and fluoroscopy.

It is of some interest that the average age in this group of patients was 53 years, and the youngest patient was 28 years old. Does chronic diaphragmatic paralysis not occur in the first three decades? Or does it occur, but symptoms not appear until the third or fourth decade?

In our institution, we have seen a much lower incidence of diaphragmatic paralysis in adults than the 17 cases in 10 years that Graham and associates report, especially since we have recognized the risks to the phrenic nerve posed by ice slush in the pericardium during open heart operations. Is symptomatic diaphragmatic paralysis more common in Liverpool, or are American physicians less sensitive to this clinical picture, and so less likely to refer such patients? I would like to ask Dr Graham if he would care to speculate on possible reasons why this syndrome seems to be even less common in this country than in Great Britain.

DR GRAHAM: I think one of the possible reasons why diaphragmatic paralysis occurs more commonly in Liverpool than it does in North America is that we have one of the highest incidences of chronic obstructive airway disease in the world. It may be that having the combination of pulmonary disease associated with diaphragmatic paralysis is more likely to cause symptoms earlier. It is a fact that symptoms do occur in young patients. Two of the patients were quite young, a 28-year-old policeman and a manual worker; I think their symptoms came to light because of their increased physical activity. This may also be one of the explanations why this condition is not seen as commonly in women as it is in men.

I would agree that a further reason why symptomatic diaphragmatic paralysis is apparently more common in the United Kingdom than in North America is the fact that it is not recognized as a cause of breathlessness.

Surgical Treatment of Automatic Atrial Tachycardias

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From 1979 to 1989, 18 patients were seen in the Electrophysiology Service, Duke University Medical Center, with automatic atrial tachycardia. There were 8 male and 10 female patients with a mean age of 28.1 ± 2.9 years. Electrophysiological mapping localized automatic foci to right atrial sites (14 patients) and left atrial sites (4 patients). Depending on origin of the focus, patients were further diagnosed as having either chronic ectopic atrial tachycardia or inappropriate sinus tachycardia. Of the 15 patients with chronic ectopic atrial tachycardia, 6 responded to medical treatment; in 9, the tachycardia was not adequately controlled. Six of them were referred for surgical intervention. All 3 patients with inappropriate sinus tachycardia underwent operative therapy. In the surgical group of patients with chronic ectopic atrial tachycardia, all 6 had a tachycardia-induced cardiomyopathy with ejection fractions ranging from 14% to 27% (mean ejection fraction, 21% ± 2.7%). Surgical techniques used (alone or in combination) included an isolation procedure in 1 patient, cryoablation in 4 patients, and excision of atrial appendages or portions of atrial free walls in 7. Normal sinus rhythm developed in all surgical patients except 1 patient who had intractable congestive heart failure preoperatively and died of this condition and stroke. The overall success rates for medical and surgical therapy were 33.3% and 88.9%, respectively ($p < 0.01$). Long-term follow-up was possible for 7 (87.5%) of 8 patients 3 to 7 years after operation. All patients with chronic ectopic atrial tachycardia were cured, but only 1 of 3 patients with inappropriate sinus tachycardia was in sinus rhythm. Compared with patients with chronic ectopic atrial tachycardia, those with inappropriate sinus tachycardia are often not cured by surgical intervention. These data show that for patients with drug-refractory automatic atrial tachycardia, surgery provides an effective and safe treatment. Because uncontrolled automatic atrial tachycardia frequently results in a dilated cardiomyopathy, early surgical intervention is recommended.

(Ann Thorac Surg 1990;49:253–60)

Automatic atrial tachycardia is an uncommon dysrhythmia resulting from either a single extranodal automatic focus (chronic ectopic atrial tachycardia) or increased automaticity of the sinoatrial node (inappropriate sinus tachycardia). Until recently, medical management has been the mainstay of treatment of automatic atrial tachycardia, but drug therapy is often unsuccessful or associated with serious side effects. With the development of new surgical techniques, patients with drug-refractory automatic atrial tachycardia can now be cured. A dilated cardiomyopathy and congestive heart failure eventually develop in many patients with sustained supraventricular tachycardia (SVT) [1, 2]. In these patients, control of the tachycardia by either medical or surgical means usually leads to improved ventricular function [1, 3, 4]. In the present study, the results of treatment in 18 consecutive patients with automatic atrial tachycardia were reviewed. In addition, results of therapy in 118 previously reported patients were analyzed.

Material and Methods

Study Group

The clinical course of all patients with automatic atrial tachycardia seen in the Electrophysiology Service, Duke University Medical Center, were reviewed. Patients with multifocal atrial tachycardia were excluded. A total of 118 patients previously reported in the literature were also available for analysis, and the results of medical and surgical therapy were compared.

Diagnosis

In general, automatic atrial tachycardia can be diagnosed using the standard electrocardiogram (ECG) followed by an electrophysiological (EP) study to confirm the site of the automatic focus. The surface ECG shows an incessant, narrow, complex SVT. In patients with inappropriate sinus tachycardia, P waves remain unchanged, and in patients with chronic ectopic atrial tachycardia, the P wave morphology differs from that seen during sinus rhythm. The "ectopic" P wave is seen to spontaneously initiate the tachycardia. A "warm-up" phase can also be identified, which is characterized by a shortening of the tachycardia cycle length over the first three to five beats to a final steady cycle length. The attempt to slow the rate using vagal maneuvers is usually unsuccessful in chronic

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Table 1. Results of Medical Treatment

Patient No.	Age (yr)	Sex	Duration	Site	Ejection Fraction (%)	Medical Treatment	Outcome	Comment
1	13	M	1 wk	Below SAN	Normal	Atenolol	SR	Previous operation for IHSS
2	63	F	1 yr	RA	79	Flecainide, metoprolol	SR	
3	21	M	5 yr	High RA	36	Digoxin, propranolol, quinidine	Intermittent SVT	Asymptomatic; declined operation
4	43	F	15 yr	Posteromedial RA	Normal	Digoxin, propranolol, quinidine	Intermittent SVT	Poor surgical candidate
5	27	F	6 yr	LA	Normal	Digoxin, propranolol	Intermittent SVT	Asymptomatic
6	15	M	1 yr	Near SAN	Normal	Propranolol, procainamide	SR	. . .
7	28	F	2 yr	High RA	41	Propranolol	SR	. . .
8	30	F	2 yr	Proximal CS	Normal	. . .	SR	. . .
9	42	F	1 yr	Low RA	Normal	Verapamil	SR	. . .

CS = coronary sinus; IHSS = idiopathic hypertrophic subaortic stenosis; LA = left atrium; RA = right atrium; SAN = sinoatrial node; SR = sinus rhythm; SVT = supraventricular tachycardia.

ectopic atrial tachycardia and inappropriate sinus tachycardia.

At the time of EP study, premature extrastimuli and rapid atrial pacing do not initiate the tachycardia, which serves to differentiate chronic ectopic atrial tachycardia and inappropriate sinus tachycardia from reentrant dysrhythmias. The tachycardia can be reset using either premature atrial extrastimuli or direct-current countershock. Rapid atrial pacing usually results in overdrive suppression with the gradual return of the original ectopic accelerated rate once pacing has been discontinued. Mapping is necessary to exclude the presence of reentry phenomena such as atrioventricular node reentrant tachycardia or concealed extranodal bypass tracts as well as to identify the site of ectopic activity to allow for possible catheter or surgical ablation [5, 6].

Study Protocol

All patients underwent EP testing to determine the cause of automatic atrial tachycardia, and initially were treated medically. Because the study span extended over 10 years, drug regimens changed according to available medications and preference of the cardiologists. Surgical intervention was recommended if the tachycardia was not adequately controlled with medication, especially to patients who had tachycardia-induced cardiomyopathy. At follow-up, patients were questioned regarding symptoms, current medications, and other treatment received in the interim since operation.

Statistical Analysis

The data were analyzed using Student's *t*-test, χ^2 analysis, or Fisher's exact test, as appropriate. A p value of less than 0.05 was considered significant.

Results

From 1979 to 1989, 18 patients, 8 male and 10 female ranging in age from 13 to 63 years (mean age, 28.1 ± 2.9 years), were diagnosed as having automatic atrial tachycardia. There were 14 right atrial and four left atrial ectopic sites (Tables 1, 2). Differences in age, sex, or location of ectopic foci were not significant between the medical and surgical groups.

One patient was not given a medical trial because it was thought his dysrhythmia could best be treated surgically. Otherwise, all patients initially received medical treatment, which was unsuccessful in 12. Three of these 12 did not undergo operation: 1 was asymptomatic, 1 had psychological problems making her a poor surgical candidate, and 1 declined surgical intervention and subsequently was lost to follow-up. A total of 9 patients underwent operative treatment with isolation procedures, cryoablation or excision of the ectopic foci, or some combination of these.

Figure 1 depicts excision of a portion of the right atrium containing a diverticulum (patient 13). The defect was easily oversewn. Excision of the sinus node was used for patients with inappropriate sinus tachycardia (Fig 2). Cryoablation was usually used for foci in areas difficult to excise (eg, around the coronary sinus or pulmonary veins) or as an adjunct to excision around the border of the resection zone (Fig 3). Of interest, patient 11 had a massively dilated heart including the right atrium. A portion of the right atrium containing the focus was excised, and the defect was repaired using a rotation flap (Fig 4).

Eight patients had an immediate successful outcome postoperatively as defined by the presence of sinus rhythm. The treatment success rate was significantly

Table 2. Results of Surgical Treatment

Patient No.	Age (yr)	Sex	Duration (yr)	Site	Ejection Fraction (%)	Medical Treatment	Surgical Procedure	Outcome	Comment
10	28	M	20	Near orifice of CS	27	Desopyramide, verapamil, atenolol	Placement of cryolesions around CS, dissection around CS	SR	Failed catheter ablation
11	20	M	2.5	Anterolateral RA	15	None	Excision of 3 × 4-cm RA free wall, defect repaired with rotation flap of RA	SR	Initially referred for cardiac transplantation
12	19	M	2.5	Junction of left inferior vein and LA	23	Digoxin, propranolol, verapamil	Placement of cryolesions over AV groove and posterior LA	SR	. . .
13	34	M	1	0.5-cm diverticulum near RA appendage	14		Excision of RA appendage including diverticulum	SR	. . .
14	16	F	1	Base of LA appendage	Low	Digoxin	Excision of LA appendage without rhythm control, ablation of AV node, insertion of pacemaker	Death (stroke) 3 days postop	Severe CHF preoperatively; arrest at anesthesia induction
15	21	M	3	Anterior LA	26	Digoxin, quinidine, propranolol, verapamil, amiodarone	Excision of LA appendage, cryoablation at base	SR	. . .
16	24	F	8	Inappropriate sinus tachycardia	Normal	Propranolol, verapamil, amiodarone	Excision of SAN	SR	. . .
17	30	F	9	Inappropriate sinus tachycardia and WPW	60	Quinidine, procainamide, desopyramide	Excision of SAN, ablation of accessory pathway	SR	. . .
18	36	F	4	Inappropriate sinus tachycardia	Normal	Dilantin (phenytoin), atenolol	Excision of SAN	SR	. . .

AV = atrioventricular; CHF = congestive heart failure; CS = coronary sinus; LA = left atrium or left atrial; RA = right atrium or right atrial; SAN = sinoatrial node; SR = sinus rhythm; WPW = Wolff-Parkinson-White syndrome.

better for the surgical group (88.9%, 8/9) than for the medical group (33.3%, 6/18) ($p < 0.01$).

Histological assessment was performed on excised portions of atrium containing the ectopic foci from 6 of the 9 surgically treated patients. Of 3 patients with chronic ectopic atrial tachycardia, only 1 had any identifiable abnormality, which consisted of focal thinning and bleb formation. Tissue excised from the 3 patients with inappropriate sinus tachycardia showed an increased number of lipofuscin-laden vacuoles by electron microscopy; otherwise sinoatrial nodal tissue was normal.

Long-term follow-up was possible for 7 of 8 surgically treated patients, all of whom were in sinus rhythm at the time of discharge. One patient with chronic ectopic atrial tachycardia was in sinus rhythm 6 months postoperatively but has since been lost to follow-up. Of 4 patients with chronic ectopic atrial tachycardia preoperatively, all continued to be asymptomatic when recently contacted 3 to 7 years after operation. Of the 3 patients with inappropriate sinus tachycardia, only 1 was free from dysrhythmia. Two new foci of SVT had developed in 1 patient, and a junctional tachycardia necessitating atrioventricular node catheter ablation and pacemaker insertion had developed in another. Of the 6 patients with chronic ectopic

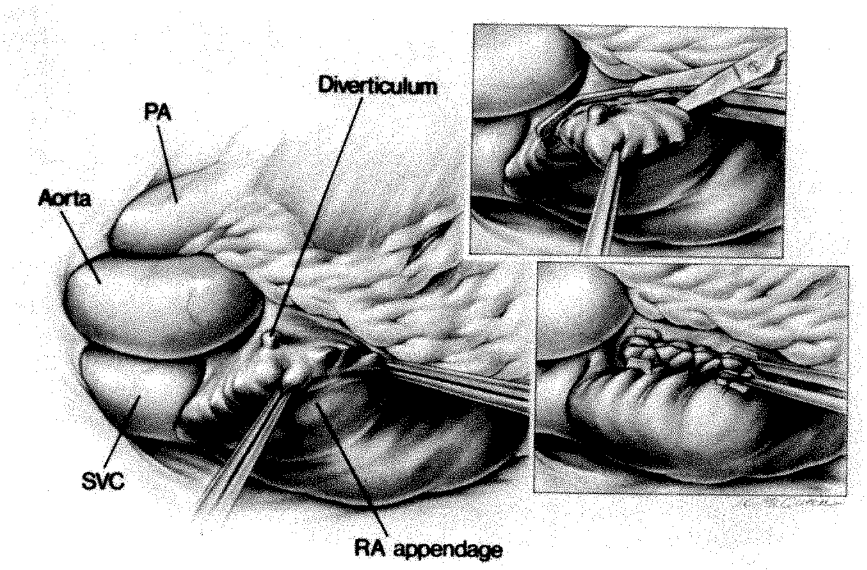

Fig 1. Focus for chronic ectopic atrial tachycardia originating in a small right atrial (RA) diverticulum. This area of atrium was easily excised and repaired without the need of cardiopulmonary bypass. (PA = pulmonary artery; SVC = superior vena cava.)

atrial tachycardia who had cardiomyopathy, 4 had follow-up radionuclide scans to assess left ventricular function. The mean preoperative ejection fraction was 19% compared with 46% 4 to 6 weeks postoperatively ($p < 0.05$).

The only death in the entire series occurred in a young girl in whom SVT developed during pregnancy. One year later, at age 16 years, she was seen with severe congestive heart failure and ectopic atrial tachycardia, which was refractory to digoxin. She underwent operation but sustained a cardiac arrest during the induction of anesthesia. The focus was thought to arise from the left atrial appendage, but despite excision of the left atrial appendage, ablation of the atrioventricular node, and pacemaker insertion, she continued to have SVT and congestive heart failure. Her clinical course suggests that she had multifocal atrial tachycardia and not automatic atrial tachycardia. She died three days postoperatively of an embolic cerebrovascular accident.

Including the present series, 136 patients with automatic atrial tachycardia have been reported [1, 2, 7–29]. Seventy-six patients underwent surgical treatment (surgical isolation or excision) with a success rate of 87% (66 patients). Assuming that all patients were treated initially with drug therapy, then the actual success rate for medical treatment is only 34% (46/136). Comparing outcome between the surgical group and medically treated overall

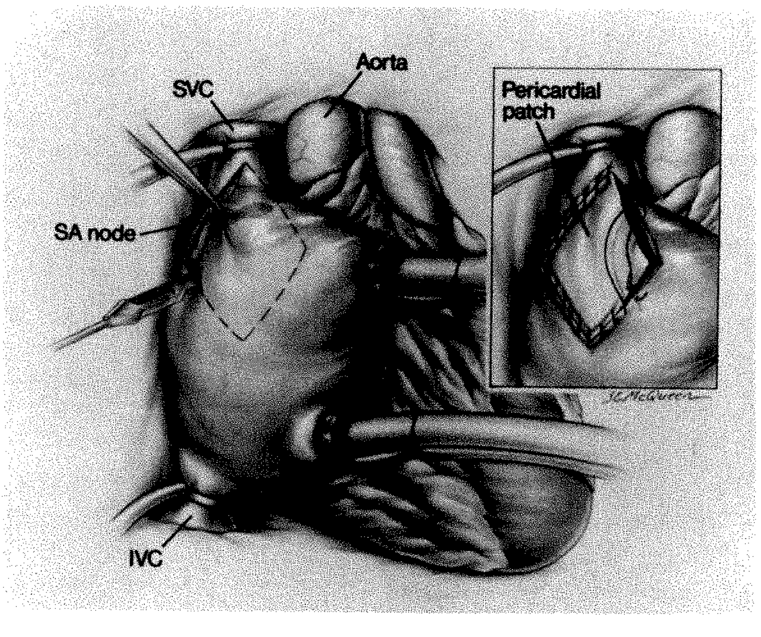

Fig 2. Excision technique applied to the sinoatrial (SA) node for treatment of inappropriate sinus tachycardia. (IVC = inferior vena cava; SVC = superior vena cava.)

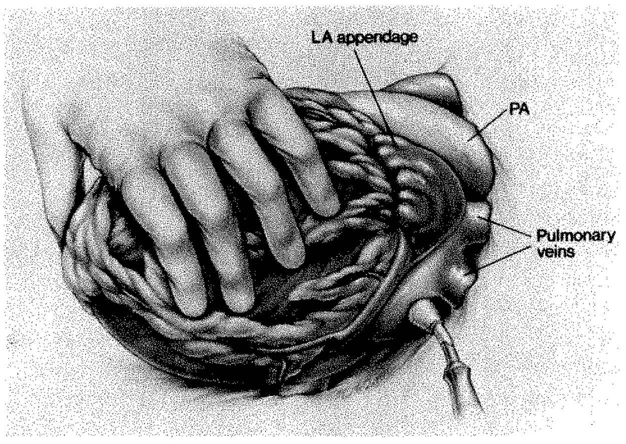

Fig 3. Cryoablation used to ablate focus near left inferior pulmonary vein. (LA = *left atrial;* PA = *pulmonary artery.)*

group, there is a significant difference favoring surgery ($p < 0.001$).

Comment

Considering all SVT, the incidence of automatic atrial tachycardia ranges between 2% and 3% in adults [6, 29] and 10% in children [5]. Automatic atrial tachycardia has been identified in all ages from infants to the elderly [2, 11]. Although it is thought to arise from an atrial automatic focus outside of the sinoatrial node or increased sinoatrial node automaticity, a localized reentry phenomenon cannot always be excluded by EP mapping [30]. Automatic atrial tachycardia can be subcategorized as chronic ectopic atrial tachycardia or inappropriate sinus tachycardia depending on the site of automaticity. Patients usually are seen with palpitations, presyncopal symptoms, syncope, or symptoms of congestive heart failure.

The development of tachycardia-induced cardiomyopathy and left ventricular dysfunction has been reported often in patients with sustained automatic atrial tachycardia [1, 5, 10, 31, 32], and thus is a major concern. The pathogenesis of this cardiomyopathy is unclear, though it may be related to a chronic depletion of myocardial high-energy phosphates [33]. In our patient population, 100% of patients (6/6) undergoing operation for chronic ectopic atrial tachycardia had left ventricular dysfunction documented before operation. Interestingly, no patient with inappropriate sinus tachycardia had a cardiomyopathy. The patients who underwent surgical intervention for chronic ectopic atrial tachycardia were therefore at higher risk for complications than those who underwent operation for other SVT syndromes (eg, ablation of accessory pathways in Wolff-Parkinson-White syndrome), a group usually quite healthy. Overall, 53.3% (8/15) of our patients with chronic ectopic atrial tachycardia had documented left ventricular dysfunction, which is comparable with the incidence of 54% to 63% previously reported [31, 34]. Elimination of tachycardia leads to improvement in the cardiomyopathy as seen in our patients who underwent postoperative left ventricular function studies.

Medical treatment with drugs is aimed at either conversion to normal sinus rhythm or control of the rapid ventricular response rate. Digoxin, propranolol hydrochloride, procainamide hydrochloride, and quinidine have all been used in different combinations with varying success rates ranging from minimal to 50% effectiveness [2, 5]. Verapamil hydrochloride [35] and amiodarone [2, 34] have also been used. Perhaps the most promising are the new class Ic drugs flecainide acetate and encainide hydrochloride, which have had successes in clinical trials for chronic ectopic atrial tachycardia [11, 18]. However, side effects such as the proarrhythmic property of these drugs may limit their long-term usefulness. The overall success rate for medication alone in the present series was only 33.3% (6/18).

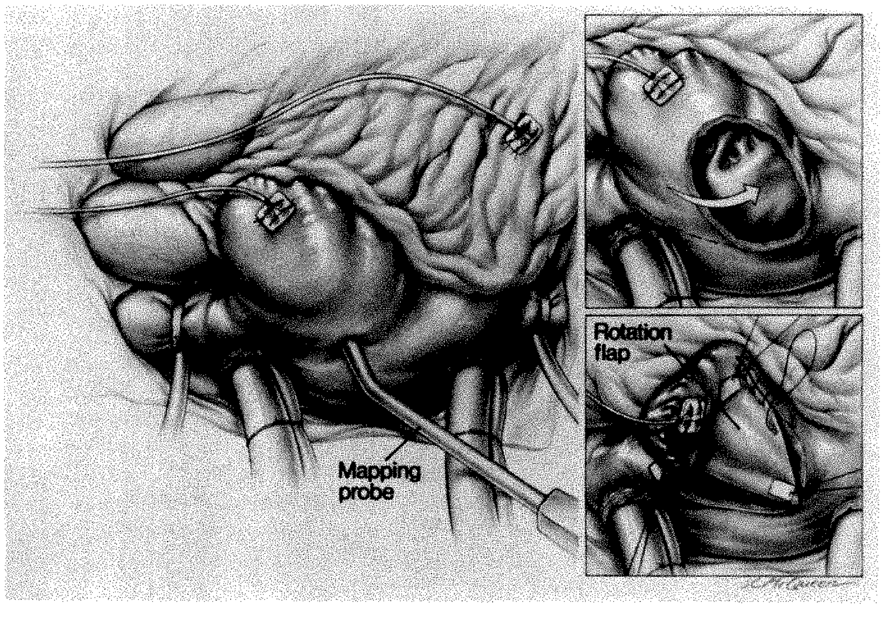

Fig 4. Focus localized to area on right atrial free wall using a bipolar probe. The area was excised and the defect repaired using a rotation flap of right atrium.

Another option being assessed for the treatment of chronic ectopic atrial tachycardia is catheter ablation. Only a few ablations have been attempted in select patients with chronic ectopic atrial tachycardia, with an overall success rate of 61.5% (8/13) [2, 7, 9, 34]. Catheter ablation currently is feasible if the focus is located in the right atrial appendage. Generally, left atrial foci are difficult to approach using catheter techniques. Finally, catheter ablation of the atrioventricular node is possible but necessitates the insertion of a permanent pacemaker, which is usually much less desirable than a directed complete ablation of the focus-producing tachycardia.

Successful surgical treatment of automatic atrial tachycardia was reported in 1973 by Coumel and colleagues [20], who used electrocoagulation and atrial septal excision for control of a focus located in the left atrium near the right superior pulmonary vein in a 15-year-old boy. Since then, numerous techniques have been developed for foci arising in different parts of the atria. The simplest is excision of an atrial appendage containing the ectopic focus. Clamping the appendage will often eliminate the dysrhythmia and confirms its origin. A focus arising in the atrial free wall can also be excised and the defect repaired with pericardium or synthetic material. The atrial septum can also be excised and repaired [16]. Isolation procedures have been developed to contain areas of ectopic activity not amenable to excision or cryoablation [36–38]. All techniques are associated with low morbidity and mortality.

The use of cryoablation alone has been criticized by Lawrie and associates [8]. In their experience, the technique has led to some failures because of either heavily trabeculated areas of the right atrium being inadequately frozen or the presence of more than one focus outside the area ablated.

Various histological findings have been identified in excised tissue bearing ectopic foci. However, no common feature has been seen that links them together. Reported abnormalities include monocyte infiltrates, focal myocyte hypertrophy, islets of fatty tissue, fibrous tissue foci, proliferation of abnormal cells, and small atrial wall aneurysms [7, 10, 12, 17, 20–25]. Tissue excised from our patients was not helpful in identifying a histological marker for chronic ectopic atrial tachycardia. However, sinoatrial nodal tissue taken from patients with inappropriate sinus tachycardia demonstrated increased lipofuscin-laden vacuoles, and this may serve as a marker for inappropriate sinus tachycardia [39].

Although surgical therapy is highly effective for patients with chronic ectopic atrial tachycardia, the outcome is less predictable for those who have inappropriate sinus tachycardia. One patient with inappropriate sinus tachycardia remains totally asymptomatic 5 years after operation. A second patient returned 3 years postoperatively with SVT related to two new ectopic atrial foci. She was found to have an electrolyte imbalance caused by diuretic abuse, which was thought to be a contributing factor. In the last patient in the series, a junctional tachycardia developed a few days after operation. It persisted for 6 years, at which time she underwent catheter ablation of the atrioventricular node and permanent pacemaker insertion. Our experience supports the findings of the group in London, Ontario [29], who noted disappointing long-term results in patients with inappropriate sinus tachycardia (or paroxysmal sinus tachycardia). It was thought that these patients might have diffuse atrial electrical abnormalities and that operation alone might not be curative.

There is no single surgical technique that can be applied to all patients with automatic atrial tachycardia. Operations must be individualized based on the site of origin of the focus for tachycardia as confirmed by intraoperative EP mapping. As EP surgery evolves, new techniques will become available for the treatment of these dysrhythmias. Treatment decisions must be made by comparing efficacy and side effects of drug therapy with the morbidity and mortality of operative therapy. Our results and those previously reported show that surgical treatment is extremely effective in patients with chronic ectopic atrial tachycardia.

Surgical cure can be accomplished with low morbidity and mortality, and should be offered to those patients whose tachycardia is not easily controlled with drugs. It should be emphasized that a dilated cardiomyopathy and congestive heart failure will eventually develop in a substantial number of patients with chronic ectopic atrial tachycardia that is not controlled. Although operative cure in those patients with tachycardia-induced myopathy results in dramatic improvement in ejection fraction, ideally patients should be referred for surgical intervention before the development of impaired ventricular function.

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DISCUSSION

DR FRED ALLEN CRAWFORD, JR (Charleston, SC): Our experience with atrial automatic tachycardias at the Medical University of South Carolina is quite similar to that of Hendry and associates. In the past 4 years, we have operated on 9 infants and children ranging in age from 1 year to 16 years. The origin of the tachycardia was right atrial in 6 patients and left atrial in 3. We have used either local or, recently, more radical excision, particularly of the right atrium, as well as cryoablation of those areas that could not be excised. We have been successful in all but 1 patient, that individual having a focus at the junction of the left inferior pulmonary vein and the left atrium that was refractory to cryoablation applied both externally and internally after hypothermic cardioplegic cardiac arrest.

One patient was a 10-month-old male infant referred for refractory atrial automatic tachycardia and severe cardiomyopathy. At the time of operation, a rhabdomyoma was obvious at the junction of the superior vena cava and the right atrium. This was excised locally and the defect was repaired with a pericardial patch. The tachycardia immediately ceased as the tumor was being excised, and the child remains well several years later. As in those patients with cardiomyopathy in the series of Hendry and associates, this child's ventricular function returned to normal after operation.

Another patient was a 4-year-old boy who was seen with refractory atrial automatic tachycardia and cardiomyopathy. At the time of operation, numerous diverticula were present in the right atrium. The automatic focus was mapped to the base of these diverticula, but because of the diffuse abnormality, the entire right atrial free wall was excised and replaced with a pericardial patch. This patient has also remained free of tachycardia.

I have several questions for Dr Hendry and his colleagues. First, have your techniques for approaching these problems changed over the years? For example, we have become much more aggressive about excision of the entire right atrial free wall in patients with automatic atrial tachycardias located on the right atrium, rather than trying to be precise and cryoablate or excise a very small specific area.

Second, elegant techniques for isolation of the right and left atrium have been described by Jim Cox from your institution and subsequently from Barnes Hospital. Your report indicates that this technique was used in 1 of your patients. Why was this method chosen, and what are your current indications for use of this technique?

We have had no experience with operation for inappropriate sinus tachycardia. What are your indications for this type of operation? In other words, what heart rate is necessary for you to consider excising the entire sinoatrial node?

Finally, your laboratory has been interested in the past in the mechanism of development of cardiomyopathy in patients with chronic tachycardias. What are your current thoughts about these mechanisms?

DR HENDRY: Concerning our technique of atrial excision, over the years the extent of excision has depended on the site of focus as identified by intraoperative mapping. We have generally used a fairly large excision; however, we have not excised the entire right atrium as you have presented.

The local isolation procedure used consisted of an undermining of the coronary sinus which was augmented by cryoablation in the same area. These local isolation procedures are used when the focus is not readily accessible by other techniques such as those adjacent to the pulmonary veins or coronary sinus. We have no experience with the procedures involving isolation of the entire right or left atrium.

As far as inappropriate sinus tachycardia is concerned, the indications for operation in these patients include a sustained heart rate greater than 120 beats/min associated with symptoms. All patients are given a trial of medical management before operation is undertaken. Cardiomyopathy has not developed in these patients in our series, compared with patients with chronic ectopic atrial tachycardias, all of whom sustained a tachycardia-induced cardiomyopathy. Therefore, in these patients with inappropriate sinus tachycardia, a longer trial of medical management might be of use. Also, because of the lower surgical success rate we will be less aggressive with this type of dysrhythmia in the future.

In our laboratory we have investigated the mechanisms of tachycardia-induced cardiomyopathy. In 1986, Dr Ralph Damiano published a report in which the implantation of atrial pacemakers in 12 dogs led to the development of cardiomyopathy. Once the pacemaker was turned off, the ejection fractions increased toward normal within a 3-week period. It is our plan to continue these investigations to try to better elucidate the actual mechanism. It has been postulated that the mechanism may be related to a depletion of high-energy phosphates within the muscle, and we intend to concentrate our studies in this area.

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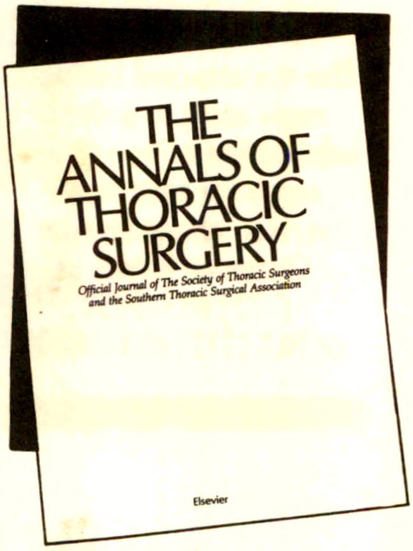
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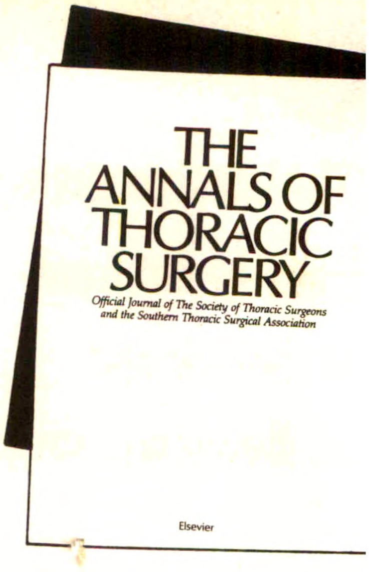
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2. Steinhaus DM, Foley LM: Atrial sensing: A continuing problem? (abstract) *PACE* 1988;11(4):533.
3. IS-1 is the designation of the standard pacing connector developed by the International Committee on Cardiovascular Implants for Surgery (International Standard Organization ISO TC150/SC).

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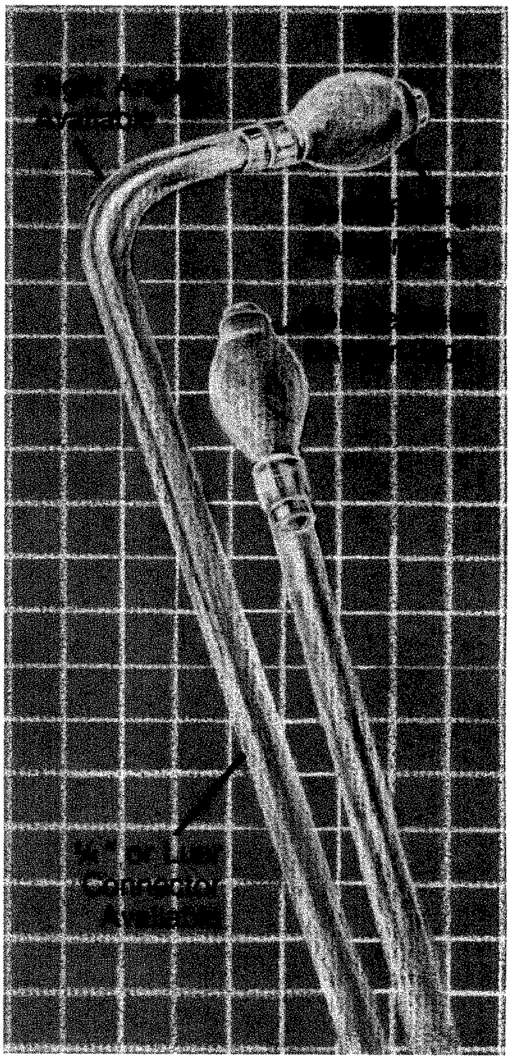

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Experience With Univentricular Support in Mortally Ill Cardiac Transplant Candidates

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Between July 1987 and March 1989, 11 patients underwent left ventricular support with the Novacor left ventricular assist system irrespective of apparent degree of right ventricular failure. The first 2 patients died of multisystem organ failure while on support. All the remaining patients survived the support period, and actuarial survival after transplantation was 100% at 6 months and 89% at 1 year. In no patient did bacterial infection develop during support or after transplantation. Right ventricular ejection fraction before implantation of the left ventricular assist system was lower than 15% in 6 of 8 patients, yet it increased twofold during left ventricular support. The need for excessive inotropic support (2 patients) or temporary (four days) mechanical right ventricular support (2 patients) while on the left ventricular support system appeared to be related to elevated pulmonary vascular resistance during support in association with large preimplantation ventricular volumes. It appears that even patients with compromised right ventricular performance can be supported long term with a left ventricular assist device. Patients with elevated pulmonary vascular resistance may require temporary right ventricular support.

(Ann Thorac Surg 1990;49:261–72)

The success of cardiac transplantation as a therapeutic modality for end-stage heart disease has stimulated an increase in the number of hospitals offering this procedure from 12 in 1983 to 131 in 1988 [1]. The increased availability of cardiac transplantation has resulted in a ninefold rise [2] in the number of transplantations performed (172 in 1983 to 1,622 in 1988). The indications for cardiac transplantation continue to expand as the procedure evolves from an experiment to a service [3]. This has placed a new demand on the available donor organs.

In 1988, nearly 25% of candidates waited between 6 months and 1 year for a suitable donor organ [4]. It is estimated that 10% to 30% of candidates will die while awaiting cardiac transplantation as the waiting period increases [5]. At the University of Pittsburgh, the need for intravenous inotropic drugs or the intraaortic balloon for support before transplantation has increased from 38% of transplant candidates in 1984 to 72% of candidates in 1988. This is due primarily to the scarcity of suitable donor hearts. Once they have received a transplant, mortally ill candidates have equal survival to elective candidates [6], but the morbidity and mortality before transplantation is especially high from infection and multisystem organ failure during this period of aggressive support [7].

The shortage of donor organs has led to a reawakening of interest in forms of chronic mechanical circulatory support. In 1985, the Working Group on Mechanical Circulatory Support from the National Heart, Lung, and Blood Institute estimated that in the United States, end-stage heart failure develops annually in 17,000 to 35,000 patients less than 70 years old, thus making them candidates for total artificial hearts (TAHs) or ventricular assist devices [8].

Since 1985, a program of bridging patients to cardiac transplantation with mechanical devices has gained growing acceptance. The device used most widely is the pneumatically powered Jarvik-7 TAH. The number of TAHs implanted increased from 37 during 1986 to 57 during 1988 [9]. Surgeons were quick to accept biventricular support for cardiac transplant candidates because conventional wisdom held that most candidates who failed traditional methods of support would have biventricular failure due either to the global nature of their cardiomyopathy or to the right ventricular failure that accompanies severe left ventricular failure. Infection was seen in approximately 50% to 70% of patients bridged to transplantation with the TAH [10, 11]. In addition, thromboembolism was reported in 5% of patients with implants.

A potential alternative to the TAH is a left ventricular assist device, which does not require excision of the native heart. Data from patients supported with many types of left ventricular assist device for acute postcardiotomy failure supported the notion that mortality from multisystem organ failure increased with isolated left ventricular support because of associated right ventricular failure [12]. Between 60% and 74% of patients bridged to cardiac transplantation between 1986 and 1988 with a ventricular assist device were supported with biventricular as opposed to univentricular devices [9].

Controversy exists in the experimental literature concerning the etiology of the right ventricular failure that

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developed in these patients. It was thought that right ventricular failure developed due either to the direct effects of aggressive left ventricular support [13, 14] or to unmasking of preexisting right ventricular failure [15, 16]. These studies established no hemodynamic or clinical criteria that could be used to determine which patients would be best served by biventricular versus univentricular support, especially in the setting of chronic heart failure. It has been thought that an adequately functioning right ventricle is necessary for successful use of isolated left ventricular assistance. No clear predictors are available, however, to determine "adequacy" of the right ventricle, which would allow the clinician to decide whether a given patient with end-stage heart disease would have adequate right ventricular performance to warrant implantation of solely a left ventricular assist device for long-term circulatory support.

Attracted by the concept of univentricular circulatory support, we conducted a prospective trial of left ventricular assistance with the Novacor left ventricular assist system (LVAS) [17]. This trial involved all cardiac transplant candidates for whom traditional means of support had failed, irrespective of the degree of right ventricular dysfunction apparent on clinical examination immediately before implantation of the device.

Material and Methods

Description of Device

The Novacor LVAS (Novacor Medical Corporation, Oakland, CA) is an electrically powered left ventricular assist system intended for long-term circulatory support in patients with end-stage heart disease [18]. In its temporary configuration it has been approved by the US Food and Drug Administration (FDA) for investigational clinical use, and as of July 1989, it has been implanted in 45 patients bridged to transplantation, 60% of whom survived to transplantation.

Protocols and Consents

All consent forms, implantation techniques, and protocols for hemodynamic and biomechanical evaluation were examined and approved by the University of Pittsburgh Institutional Review Board. An investigational device exemption was granted by the FDA, and the clinical trial was begun in July 1987. Informed consent was obtained from all patients or the next of kin. All support patients were candidates for orthotopic cardiac transplantation and underwent such transplantation as soon as a donor organ could be found and it was clear that they had no contraindication to transplantation.

Patient Selection

All patients who were candidates for cardiac transplantation at the University of Pittsburgh between July 1, 1987, and February 28, 1989, were potential candidates for LVAS support. Indications for LVAS implantation included signs of end-organ hypoperfusion typified by rising serum blood urea nitrogen and creatinine levels with urine output that was increasingly unresponsive to diuretics, depressed level of consciousness, cool extremities, low blood pressure, pulmonary edema reflected on the chest radiograph, or unstable cardiac rhythm. When these findings occurred during maximally tolerable inotropic or intraaortic balloon pump support and a donor heart was not available, the patient was assessed independently by two cardiologists and two surgeons. If they were in agreement, the LVAS was implanted.

During the study period, 4 patients were seen in acute cardiogenic shock from acute myocardial infarction. Because of the inherent cardiac instability of 2 of these patients and right coronary infarction in the 2 others, these candidates were deemed inappropriate for LVAS support, and the Jarvik-7 TAH was implanted instead of the Novacor LVAS. Another concern when the myocardium was infarcted was the uncertain ability of the freshly infarcted ventricle to support the sutures used to secure the inflow conduit. Other contraindications to mechanical support included overt sepsis, a positive blood culture within five days, serum creatinine level greater than 3 mg/dL, progressive unstable hepatic function, a cerebrovascular accident within 2 weeks, and pulmonary infarction or embolism within 4 weeks.

During the 20 months of the study, 110 patients received orthotopic heart transplants, 11 (10%) of whom qualified for LVAS support. The mean age of the 11 patients was 47 years (range, 21 to 63 years), and there were 10 men and 1 woman (Table 1). Four patients had ischemic cardiomyopathy, 5 had idiopathic cardiomyopathy, and 2 had familial cardiomyopathy. Two of the patients with ischemic cardiomyopathy had chronic unstable angina with coronary artery disease not amenable to bypass grafting, and the 2 others had severe left ventricular myocardial infarctions after percutaneous coronary angioplasty. Body surface area ranged from 1.59 to 2.24 m^2 (mean area, 1.91 m^2).

All patients were on a regimen of inotropic support, the mean duration of which was 29 days (range, 8 to 71 days). Inotropic regimens included combinations of dopamine hydrochloride, dobutamine hydrochloride, amrinone lactate, and epinephrine; 8 patients were receiving at least three of these drugs and all patients, at least two. Nine patients were supported on the intraaortic balloon for an average of 11 days (range, two to 33 days). Two patients could not be so supported; patient 2 had peripheral vascular disease, which made intraaortic balloon insertion hazardous, and in patient 9, the intraaortic balloon was in place for two days, but was removed three days before LVAS implantation because a heart rate greater than 140 beats per minute and two episodes of ventricular fibrillation requiring direct-current countershock made balloon timing impossible. Seven patients had severe ventricular tachyarrhythmias requiring either direct-current countershock or lidocaine hydrochloride infusion just before LVAS insertion.

The average left ventricular ejection fraction determined by multiple gated nuclear scanning techniques before support was 16% (range, 8% to 23%), and the average cardiac index was 1.9 L/min/m^2 (range, 1.4 to 2.4 L/min/m^2). Pulmonary edema was suggested by the chest radiographs of all patients, and 4 patients had a serum creatinine level of 2.0 mg/dL or greater prior to support.

Table 1. Preoperative Patient Data

Patient No.	Sex	Age (yr)	Diagnosis (cardiomyopathy)	Body Surface Area (m^2)	Ventricular Rhythm Before Implantation	Duration of Support Before Novacor System (days)		Total Serum Creatinine (mg/dL)	Total Serum Bilirubin (mg/dL)	Left Ventricular Ejection Fraction (%)	Cardiac Index (L/min/m^2)
						Inotropic Agents	IABP				
1	M	55	Idiopathic	2.1	VT	9	6	1.5	1.8	8	2.2
2	M	63	Ischemic	1.9	None	32	0	2.2	9.0	16	1.8
3	M	63	Idiopathic	1.9	VT/Fib	23	5	1.3	2.6	15	1.4
4	M	55	Ischemic	1.7	VT	22	30	1.4	0.9	23	1.8
5	M	48	Ischemic	2.2	None	9	7	1.1	0.7	17	2.4
6	M	43	Idiopathic	2.1	VT	43	5	0.8	1.1	12	1.7
7	M	56	Ischemic	1.7	None	36	33	2.1	1.1	20	2.2
8	F	23	Familial	1.6	None	23	9	1.9	2.1	18	1.8
9	M	46	Idiopathic	2.1	VT/Fib	71	0	2.1	1.7	11	1.7
10	M	21	Idiopathic	1.9	VT	8	2	2.3	1.9	12	1.8
11	M	39	Familial	1.8	Premature ventricular contractions	37	22	0.9	. . .	20	1.7

IABP = intraaortic balloon pump; VT = ventricular tachycardia; VT/Fib = ventricular tachycardia leading to arrest.

Patients 2 and 3 had severe passive congestion of the liver as reflected by a rise in the total serum bilirubin level. All but patient 2 had changes in mental status ranging from mild impairment of mental aptitude tests in 3 patients to frank drowsiness in 7. All patients were systemically anticoagulated with intravenously administered heparin sodium preoperatively except for patient 8. No patient had more than minimal tricuspid regurgitation detectable on two-dimensional echocardiography.

Implantation Technique

A median sternotomy was performed and the incision extended to the umbilicus. A pocket was made in the left upper quadrant between the costal margin and the iliac crest in the plane between the posterior rectus sheath and the rectus abdominis muscle and extending laterally between the internal oblique and transversus abdominis muscles.

The inflow and outflow conduits were preclotted using the patient's blood mixed with a unit of cryoprecipitate and 20 mL of activated thrombin (thrombin + 10 mL of calcium chloride). The outflow conduit was then anastomosed end-to-side to the ascending aorta. Prosthetic valves were inserted into the pump, the inflow conduit and outflow conduits were connected to the pump, and the pump was filled with saline solution. The inflow conduit was tunneled under the costal margin and brought out through the pericardium near the reflection of the diaphragm onto the chest wall. Using a special trocar, the vent tube was tunneled inferior to the umbilicus and brought out through the skin near the right anterior superior iliac spine. The pump was then placed into the subrectus pocket.

The patient was heparinized and placed on full normothermic cardiopulmonary bypass. Bicaval cannulation was used in the majority of patients to allow caval snaring and inspection of the interatrial septum for a potential patent foramen ovale. After the right atrium was closed, a left atrioventricular vent was inserted through the right superior pulmonary vein, and the apex of the heart was lifted up and encircled with pledgeted horizontal mattress sutures to secure the apical connector ring. The apical myocardium was excised within the connector ring, and the left ventricle was examined for mural thrombus. The inflow conduit was secured within the connector ring, and the heart, pump, and conduits were purged of air. Cardiopulmonary bypass was then discontinued while the Novacor LVAS started. Inotropic drugs were used as required to support the right ventricle. Protamine sulfate was given to reverse heparinization, and platelets, fresh frozen plasma, and cryoprecipitate were given to reverse any residual coagulopathy.

Patient Management

Anticoagulation was usually withheld during the first 24 hours until chest drainage had stopped or decreased to less than 100 mL per eight hours. In patients 5, 6, 8, 9, 10, and 11, intravenous administration of heparin was begun within 48 hours of support with the goal, over the next 24 hours, of a partial thromboplastin time of approximately 1.5 times control. In patients 3, 4, and 7, heparin administration was started between days 3 and 5. In the period without heparin, patients received either dipyridamole (Boehringer Ingelheim, Ridgefield, CT), 75 mg every eight hours, or intravenous low molecular weight dextran. In the event of recurrent bleeding or cardiac tamponade, anticoagulant administration was stopped for two to three days until it was thought that there was no danger of new bleeding. In patients 3, 4, 8, 9, and 11, administration of oral warfarin sodium (DuPont, Inc, Wilmington, DE) was begun between the first and second week of support as heparin administration was stopped, thus increasing the prothrombin time to 1.5 times control.

Prophylactic antibiotics were given as soon as it was determined that a patient was a candidate for LVAS support. The regimen, which was continued after implantation, consisted of 250 to 500 mg of intravenous vancomycin every six hours until all lines were removed; an oral elixir of nystatin (2 million units), gentamicin sulfate (80 mg), polymyxin E (100 mg), and vancomycin (60 mg) every six hours; and a mixture of Orabase paste of 2% nystatin, 2% gentamicin, 2% polymyxin E, and 2% vancomycin applied to the buccal mucosa every six hours while the patient was intubated.

Pharmacological support was continued postoperatively as required for maintenance of normal peripheral resistance (Neo-Synephrine [phenylephrine hydrochloride], sodium nitroprusside, and nitroglycerin) and right ventricular contraction (Isuprel [isoproterenol hydrochloride], dopamine, dobutamine, or epinephrine). In addition, prostaglandin E_1 was used temporarily in patients 3, 7, and 11 for reduction of pulmonary vascular resistance.

Patients were managed in the surgical intensive care unit until they were extubated and all invasive lines and drainage tubes were removed, at which point they were transferred to a private room on the transplant unit.

Hemodynamic and Biomechanical Monitoring

Immediately before induction for LVAS implantation, a rapid-response thermodilution catheter (American Edwards, Santa Ana, CA) was placed percutaneously into the pulmonary artery through the right internal jugular vein. A static hemodynamic profile consisting of heart rate, mean arterial pressure, central venous pressure, systolic, diastolic, and mean pulmonary artery pressures, and pulmonary capillary wedge pressure was made along with cardiac output. The cardiac output computer and catheter were capable of determining stroke volume, end-systolic and end-diastolic volumes, and right ventricular ejection fraction (RVEF). Total pulmonary resistance was calculated by multiplying the mean pulmonary artery pressure by 80 and dividing by the cardiac output. These measurements were made immediately after induction of anesthesia and at 20, 40, and 60 minutes after discontinuation of cardiopulmonary bypass (start of the LVAS). In addition, they were repeated at the time of chest closure and 8, 24, and 48 hours after LVAS start-up. A final set of measurements was obtained after induction of anesthesia for cardiac transplantation. At least three separate measurements were averaged for each data record to minimize error. A full set of these hemodynamic measurements was available for patients 4 through 11.

Biomechanical data were acquired under the direction of two of us (H.S.B. and J.F.A.) after the pericardium was opened but before LVAS implantation, and again before chest closure after the LVAS was implanted. A pair of 2-mm piezoelectric crystals (model 1-1010-5H; Vernitron, Bedford, OH) modified by one of us (J.F.A.) was placed subepicardially at the intersection of the long and short axes of the free wall of the right ventricle, midway between the infundibulum and acute margins of the right ventricle, as described by Morris and Wechsler [19]. A special insertion tool ensured proper location and alignment of the transducers within the myocardium [20]. These crystals coupled with a sonomicrometer (model 120; Triton Industries, San Diego, CA) measured segmental changes along the long axis of the right ventricular free wall.

A 5F high-fidelity microtip catheter (Millar MPC-500; Millar Instruments, Houston, TX) connected to a control unit (model TCB-500) was placed into the lumen of the right ventricle via the tricuspid valve through a pursestring suture in the right atrium. Simultaneous pressure–length data were acquired on an IBM PC-AT computer during steady-state conditions and during gradual occlusion of the inferior vena cava both before and after LVAS implantation. Each data sample consisted of a 15-second sample of pressure–dimension data acquired at 256 Hz. The steady-state set provided information about "ejection phase" indices of baseline contractility [21] such as peak rate of rise of right ventricular pressure, peak velocity of fiber shortening, and fractional fiber shortening. Other derived variables included segmental stroke work and segmental power output, defined as stroke work times heart rate divided by minimal segment length during inferior vena cava occlusion. The data obtained during vena cava occlusion allowed stroke work to be normalized to preload end-diastolic length.

Results

Nine (82%) of the 11 patients who received an LVAS implant survived support to reach the goal of orthotopic heart transplantation (Table 2). Patient 1 died during operation of complications of massive blood loss (4,610 mL), loss of peripheral vasomotor tone, and refractory right ventricular failure. In this patient, the inflow and outflow conduits had not been preclotted. Patient 2 survived the implantation procedure, but sustained a large blood loss (15,710 mL) because of the amount of surgical dissection associated with bilateral internal mammary artery bypass grafts he had received 5 years previously. Both internal mammary arteries were transected during the dissection, and this contributed to some degree of cardiac failure necessitating cardiopulmonary bypass for completion of dissection. This patient ultimately died of right heart failure, multisystem organ failure, and cardiac arrest.

The time required for surgical implantation of the LVAS in the 9 patients who survived this procedure averaged 5 hours 48 minutes (range, five to 11 hours). The average cardiopulmonary bypass time was 62 minutes (range, 40 to 88 minutes). The period of LVAS support in these patients averaged 38 days (range, two to 125 days).

All 9 patients who underwent transplantation survived the procedure and were discharged from the hospital. All patients are alive except patient 6, who died 6 months after transplantation secondary to complications from non-A, non-B hepatitis, cytomegalovirus gastritis, cryptococcal meningitis, and pseudomembranous enterocolitis.

Table 2. Outcome for Patients Supported With the Novacor Left Ventricular Assist System

Patient No.	Cardiopulmonary Bypass Time	Surgical Time	Length of Support (days)	Transplantation	Outcome
1	4'24"	14'00"	0	No	Died in operating room
2	2'31"	12'00"	23	No	Died in intensive care unit
3	48"	5'18"	61	Yes	Home; alive
4	60"	6'17"	10	Yes	Home; alive
5	60"	6'35"	7	Yes	Home; alive
6	57"	7'00"	72	Yes	Home; alive
7	1'20"	7'25"	33	Yes	Died at 6 mo
8	61"	6'30"	15	Yes	Home; alive
9	1'28"	11'00"	125	Yes	Home; alive
10	40"	11'00"	2	Yes	Home; alive
11	64"	10'00"	18	Yes	Home; alive

Complications

Complications that occurred during support are listed in Table 3. Patients 2, 3, and 8 had evidence of cardiac tamponade within 48 hours of LVAS implantation, manifested by poor filling of the pump and decreasing cardiac output with increased central venous pressures, which were relieved by surgical drainage. Patients 4, 7, and 11 had delayed cardiac tamponade that required surgical drainage between seven and 12 days after LVAS implantation. The average combined intraoperative and postoperative blood loss was 5,367 mL (range, 550 to 16,000 mL). Patient 9 had dehiscence of the rectus muscle fascia over the Novacor pump on day 23, leading to arterial bleeding and expansion of the pump pocket. This was repaired by drainage and direct repair of the fascia.

Three patients were found to have a patent foramen ovale. In patient 4, it was closed electively on inspection of the interatrial septum at the time of LVAS implantation. In patients 3 and 7, it was found and closed within 24 hours of operation after a low arterial oxygen saturation in the intensive care unit prompted cardiac catheterization and dye-dilution studies.

Transient cerebral ischemic episodes were seen in patients 3 (days 21 and 53), 6 (days 43, 45, and 49), and 7 (days 29 and 32). These episodes were short-lived (minutes) and most commonly involved visual disturbances, paresthesia of the limbs, and speech deficits. Patients 3 and 6 had minor completed strokes on days 51 and 32, respectively. Of all patients with neurological problems, only patient 3 had any residual neurological deficit.

There were no infections during the period of support in any patient. However, patient 7 sustained a fatal viral infection after transplantation (Table 4). Other infections were typical of the transplant population at our institution except for the gram-negative septicemias seen early after transplantation in patients 5 and 6 (day 5 and day 9,

Table 3. Complications

Patient No.	Blood Loss (mL)	Tamponade (post-op day)	PFO Closure (day)	TIA (postop day)	CVA (postop day)	RV Failure; Type of Support	Other
1	4,610	NA	NA	NA	NA	NA	Vasodilatation
2	15,710	2	None	None	None	Yes; inotropic	Multiorgan failure
3	2,750	1 (2 times)	1	None	21, 53	Yes; inotropic	. . .
4	7,225	7	0[a]	None	None	No	. . .
5	1,965	None	None	None	None	No	. . .
6	2,875	None	None	43, 45, 49	51	No	. . .
7	8,280	12	1	29, 32	None	No	. . .
8	16,000	1	None	None	None	Yes; ECMO[b]	ARDS
9	900	None	None	None	None	Yes; RVAD	Abdominal dehiscence, day 23
10	2,575	None	None	None	None	Yes; inotropic	. . .
11	550	10, 12	None	None	None	Yes; inotropic	. . .

[a] This patient had elective closure in the operating room. [b] This patient received right atrial to left atrial ECMO.

ARDS = adult respiratory distress syndrome; CVA = cerebrovascular accident (completed cerebral stroke); ECMO = extracorporeal membrane oxygenation; NA = not applicable; PFO = patent foramen ovale; RV = right ventricular; RVAD = right ventricular assist device; TIA = transient ischemic attack.

Table 4. Infections After Transplantation

Patient No.	Infection	Location	Organism	Post-operative Day
1	NA	NA	NA	NA
2	NA	NA	NA	NA
3	Yes	Lung	Mixed	64
4	Yes	Meninges	*Cryptococcus*	274
		Esophagus	Cytomegalovirus	274
5	Yes	Blood	*Enterobacter*	5
6	Yes	Blood	*Serratia*	9
		Blood	*Serratia*	30
7	Yes	Meninges	*Cryptococcus*	11
		Stomach	Cytomegalovirus	35
		Colon	*Clostridium difficile*	35
		Liver	Non-A, non-B hepatitis	118
		Lung	*Klebsiella*	148
8	No	. . .	. . .	. . .
9	No	. . .	. . .	. . .
10	Yes	Sinus	Mixed	75
11	Yes	Systemic	Cytomegalovirus	35

NA = not applicable.

respectively). These were presumed to have been secondary to venous access lines, as symptoms cleared with removal of the lines and antibiotic therapy.

Hemodynamics

Complete hemodynamic studies were available on patients 4 through 11. Although all 8 of these patients survived LVAS support and underwent successful transplantation, they could be classified according to the ease with which inotropic support for the right ventricle could be discontinued or decreased within the first 48 hours of support. Inotropic requirement was thus arbitrarily expressed as inotropic equivalents (IEs), where 1 μg/kg/min of dopamine or dobutamine represented 1 IE and 0.1 μg/kg/min of epinephrine or norepinephrine represented 10 IEs.

Group A included patients 4 through 7, who were receiving an average of 15 IEs of support at the time of sternal closure and 4 IEs after 48 hours of support. Group B included patients 8 through 11, who were receiving an average of 83 IEs at sternal closure. Two patients in group B (patients 8 and 9) required mechanical support of the right ventricle within 12 hours of LVAS support, and patients 10 and 11 were still receiving an average of 17 IEs at 48 hours.

Patients in groups A and B could be further subdivided into two categories (A_1, A_2, B_1, and B_2) based on initial data and the subsequent response of the right ventricle to LVAS support. Figure 1A displays the RVEF data for the four groups of patients, and Figure 1B shows the corresponding IE requirements in these groups. Patients 5 and 7 (group A_1) had RVEFs that were essentially normal (greater than 20%) at the start of LVAS support and remained normal or increased slightly throughout the course of support. Inotropic requirements for the right ventricle in this group gradually decreased to minimal amounts by 48 hours of support. Both patients had ischemic cardiomyopathy. Patients 4 and 6 (group A_2) had RVEFs that were subnormal (less than 20%) before LVAS support but quickly increased to the normal range after start of support while inotropic requirements rapidly decreased. Patient 6 had an increase in RVEF from 7% before support to 53% after 72 days of support.

All patients in group B had RVEFs that were in the range of 10% before LVAS support and that increased only marginally during early LVAS support. Also, these patients were characterized by increasing IE requirements up to eight hours after LVAS insertion. All of these patients had idiopathic or familial cardiomyopathy. By 24 hours after insertion, patients 10 and 11 (group B_1) showed only minimal if any change in the RVEF but had

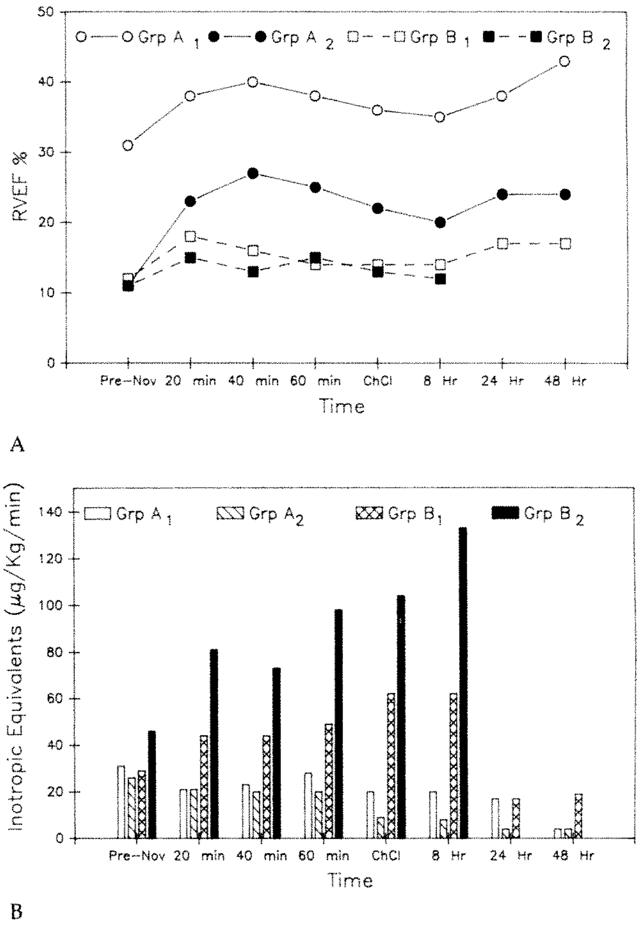

Fig 1. (A) Right ventricular ejection fraction (RVEF) before (Pre-Nov) and during support with the Novacor left ventricular assist system (LVAS). (B) Inotropic requirement, expressed in inotropic equivalents (IEs) before and during LVAS support: 1 μg/kg/min of dopamine hydrochloride or dobutamine hydrochloride = 1 IE, and 0.1 μg/kg/min of epinephrine or norepinephrine = 10 IEs. Group B_2 required mechanical right ventricular support within 12 hours after LVAS support was initiated. See text for discussion of groups. (ChCl = chest closure.)

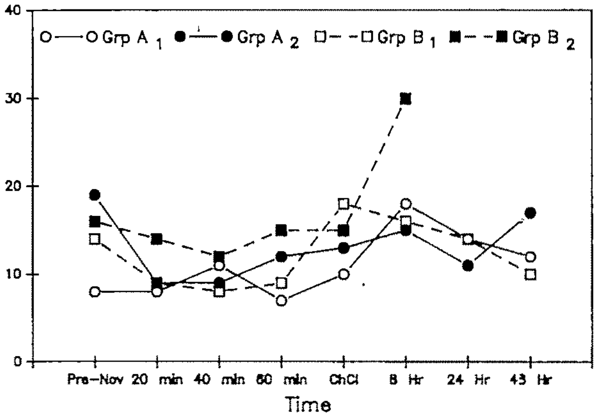

Fig 2. Central venous pressure measured before and during support with the Novacor left ventricular assist system. Time abbreviations are the same as in Figure 1.

a reduced need for inotropic support. In contrast, patients 8 and 9 (group B_2) showed a corresponding increase in the need for inotropic support over the first eight hours of LVAS support and required mechanical right ventricular support by 12 and nine hours after LVAS implantation, respectively. Patient 8 had unresolving adult respiratory distress syndrome after LVAS implantation with a large alveolar-arterial oxygen gradient, and underwent right atrial to left atrial extracorporeal membrane oxygenation for four days. With clearing of the chest radiograph, extracorporeal membrane oxygenation was discontinued and LVAS support alone was continued for 11 more days. In patient 9, severe pulmonary hypertension developed, presumably secondary to transfusion of blood products for bleeding, and necessitated right ventricular support with a centrifugal pump from the right atrium to the pulmonary artery for four days. This patient was supported for the longest period in this series, and showed a remarkable recovery of right ventricular performance with an RVEF of 57% after 125 days of support.

In an effort to explain the changes seen in RVEF in this population, other hemodynamic data obtained through the RVEF catheter were examined. The LVAS afforded an immediate rise in cardiac index of 30% to 40% in all groups of patients, and cardiac index was maintained at a level between 2.5 and 3.0 L/min/m^2. Patient 8 had only a small rise (5%) in cardiac index when the LVAS was started, and it was only after a large amount of inotropic support that her cardiac index rose to 2.5 L/min/m^2. The central venous pressure dropped slightly in all groups from a presupport level of 8 to 20 mm Hg to 8 to 16 mm Hg after support except in group B_2. In that group, central venous pressure rose to 30 mm Hg just before mechanical right ventricular support (Fig 2).

A drop in pulmonary capillary wedge pressure from near 30 mm Hg to near 10 mm Hg was produced and maintained by the LVAS in all groups, as shown in Figure 3A. The resultant drop in mean pulmonary artery pressure is depicted in Figure 3B. Patients in both group A and group B had similar reductions in mean pulmonary artery pressure at the onset of LVAS support, but there was much variability in pulmonary artery pressure after the patients left the operating room.

Changes in total pulmonary resistance are shown in Figure 3C. Although all groups showed a 40% to 60% drop in total pulmonary resistance, group B patients showed a progressive rise in resistance toward presupport levels by the time the chest was closed. Whereas group B_1 patients showed a gradual return to normal pulmonary resistance, group B_2 patients continued to show a rise in resistance up to the time of mechanical support.

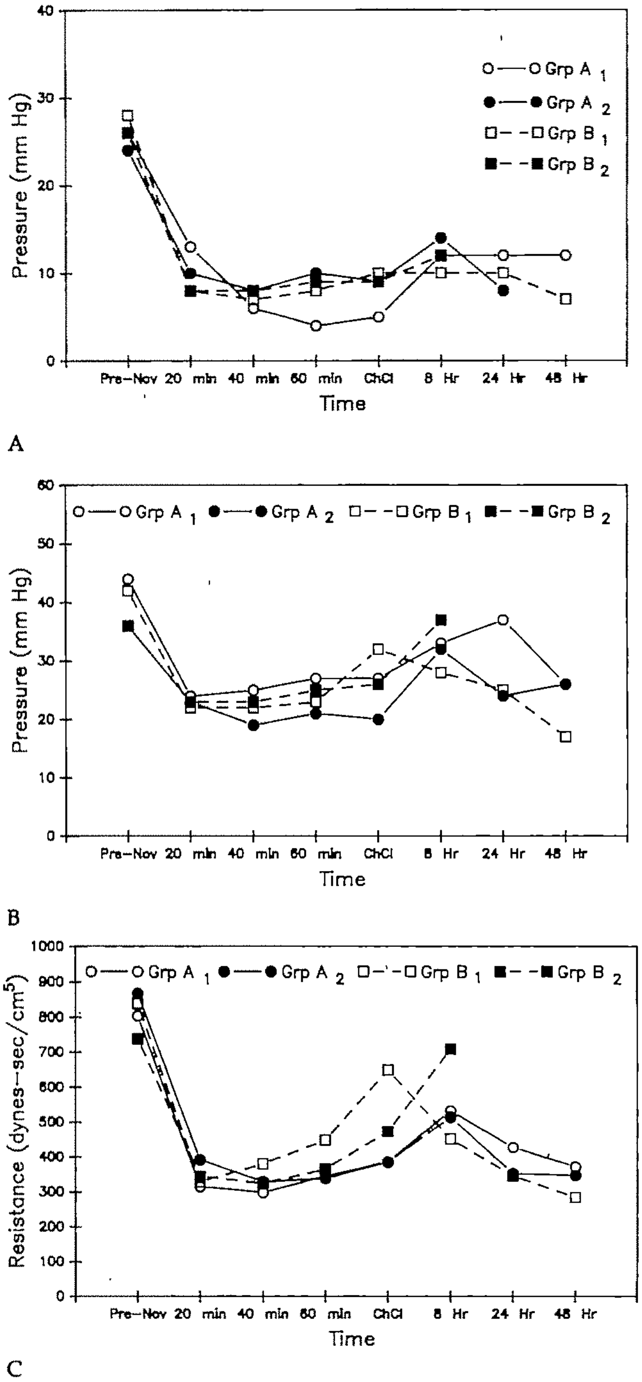

Fig 3. (A) Pulmonary capillary wedge pressure, (B) mean pulmonary artery pressure, and (C) total pulmonary resistance measured before and during support with the Novacor left ventricular assist system. Time abbreviations are the same as in Figure 1.

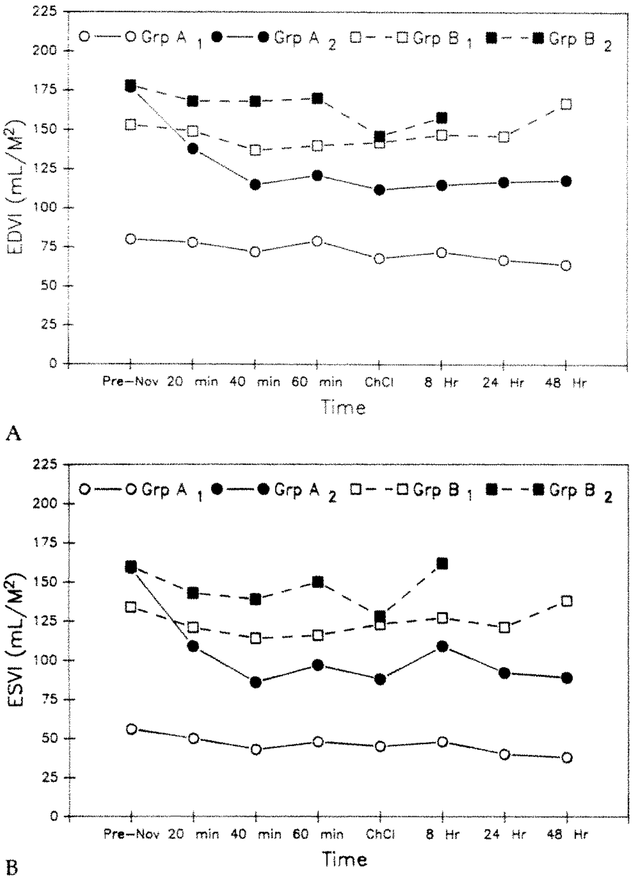

Fig 4. (A) End-diastolic volume indices (EDVI) and (B) end-systolic volume indices (ESVI) for the right ventricle before and during support with the Novacor left ventricular assist system. Time abbreviations are the same as in Figure 1.

Figure 4A shows right ventricular end-diastolic volume indices (RVEDVIs) obtained by the RVEF catheter, and Figure 4B illustrates the corresponding end-systolic volume indices (RVESVIs) for the four groups. Group A_1 patients had the smallest RVEDVI and RVESVI, 75 mL/m^2 and 50 mL/m^2, respectively. Over the first 48 hours of support RVEDVI dropped by approximately 10% to 15% and RVESVI, by 15% to 30%. Although the largest right ventricular volumes before implantation in the group A patients were in group A_2, a reduction of RVEDVI of 30% to 40% and RVESVI of 35% to 45% occurred with LVAS support. Group B patients also had large right ventricular volumes before LVAS support; however, RVEDVI and RVESVI dropped by less than 10% for group B_1 patients and actually increased slightly by 48 hours of support. Group B_2 patients had the largest preimplantation right ventricular volumes and showed the least change in right ventricular volume with LVAS support.

Biomechanical Measurements

Table 5 contains biomechanical data obtained via sonomicrometry before LVAS implantation and just before chest closure after implantation of the LVAS. Group A_1 patients demonstrated a significant decrease in peak right ventricular pressure and fractional fiber shortening. End-diastolic length decreased, and there was no change in

Table 5. Biomechanical Indices[a,b]

	Group A_1			Group A_2			Group B_1			Group B_2		
Index	Before	After	*p* Value	Before	After	*p* Value	Before	After	*p* Value	Before	After	*p* Value
Segmental power output	267 ± 108	268 ± 75	NS	−43	123	<0.01[c]	489 ± 48	392 ± 56	<0.005[d]	434 ± 99	369 ± 84	<0.005[d]
Fractional fiber shortening	0.19	0.10	<0.01[c]	0.03	0.11	<0.01[c]	0.19 ± 0.02	0.18 ± 0.02	NS	0.13 ± 0.02	0.15 ± 0.03	NS
Peak ventricular pressure	49	30	<0.01[c]	39	29	<0.01[c]	32 ± 1.2	38 ± 0.4	<0.005[d]	43	31	<0.01[c]
RVEDL	10.5	8.1	<0.01[c]	17.6	15.5	<0.01[c]	15.5 ± 0.2	14.9 ± 0.4	<0.005[d]	13.8	16.3	<0.01[c]

[a] See text for discussion of groups. [b] *Before* means before implantation of the left ventricular assist system, and *after* means after implantation of the system and just prior to chest closure. [c] Significance was obtained by sign rank test for paired observation. [d] Significance was obtained by paired *t* test.

NS = not significant; RVEDL = right ventricular end-diastolic length.

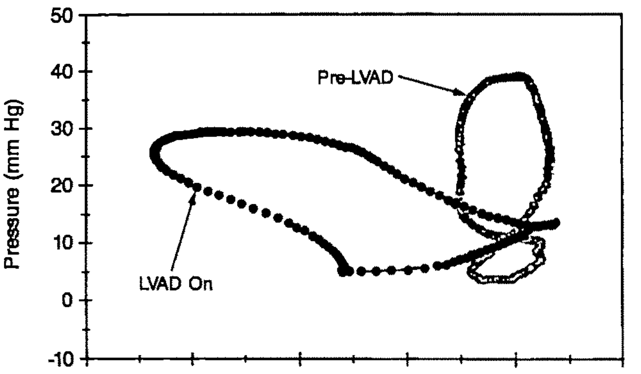

Fig 5. Right ventricular pressure–segment length "work" loops for a patient before and during support with the Novacor left ventricular assist device (LVAD).

segmental myocardial power output. Group A_2 showed a dramatic increase in myocardial power output and fractional fiber shortening along with a reduction in peak ventricular pressure and end-diastolic length. Groups B_1 and B_2 showed a decrease in segmental myocardial power output with no significant change in fractional fiber shortening. Peak ventricular pressure decreased in all but 1 of the group B patients. End-diastolic length decreased slightly in group B_1 but increased in group B_2 patients, who required mechanical right ventricular support.

Figure 5 shows a typical ventricular pressure–segmental length loop for patient 6 (group A_2) before and after LVAS implantation. These loops demonstrate how little change in ventricular dimension occurred during a cardiac cycle before the LVAS was implanted and how much more ventricular motion was seen once the LVAS was started. Figure 6 displays the segmental work–end-diastolic length relationship obtained during vena cava occlusion for patient 6 before and during LVAS support. Before the LVAS was implanted, changes in preload did not effect much change in myocardial work, whereas after implantation, the ventricle was able to respond over a wider range of preloads.

Comment

The goal of this trial was to apply univentricular support to a wide spectrum of patients with end-stage cardiomyopathy irrespective of the amount of right ventricular failure present before implantation. As can be seen from Table 1 and Figure 1A, this series included patients with varying degrees of right ventricular failure (RVEFs ranging from 10% or less to as high as 30%) and varying causes of cardiomyopathy. Many of these patients clearly would have been considered candidates for the TAH based on gross cardiomegaly with elevated left and right atrial pressures. Indeed, in 5 of the 8 patients on whom we collected hemodynamic data, the RVEDVI was greater than or equal to 150 mL/m^2. Thus, this trial represents an important departure from current conventional wisdom concerning univentricular support.

Several major points can be made about this group of patients as opposed to our patients supported with the TAH. First, all but the first 2 patients in this trial were able to undergo transplantation and were discharged home. The first 2 patients presented technical problems and represented problems in patient selection.

Second, we did not see any bacterial infections in this group during the period of support or after transplantation despite multiple sternotomies in 6 patients for postoperative bleeding and tamponade, which continues to be a vexing problem with mechanical support of the heart. This lack of septic complications may be related to a perioperative regimen of intestinal sterilization, which plays an important role in preventing translocation of intestinal bacteria during low-perfusion states [22]. Another factor leading to a low infection rate may be the preservation of the native heart, thereby avoiding local effects of biomaterials on white blood cells in the mediastinum [23]. The incidence of bloodborne viral infection after transplantation is of concern and may be related to blood transfusions necessary during the implantation procedure. Although 3 patients had transient cerebral deficits while on LVAS support, 2 of them failed to receive any anticoagulants or antiplatelet therapy until five days after LVAS implantation because of problems with bleeding and tamponade. Only 1 of these patients had any permanent residual neurological deficit.

Examination of the hemodynamic data reveals that none of the intracardiac pressure measurements (central venous pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure) made before implantation was able to predict which patients would have a more favorable outcome with univentricular support. In addition, only 2 of the 8 patients had RVEF measurements that were much greater than 10% before LVAS implantation. All patients had an equally dramatic reduction of the pulmonary capillary wedge pressure secondary to left ventricular decompression, followed by an equally uniform initial reduction in mean pulmonary artery pressure. The central venous pressure dropped with LVAS implantation in most patients and ranged between 10 and 15 mm Hg except in the patients who required mechanical right

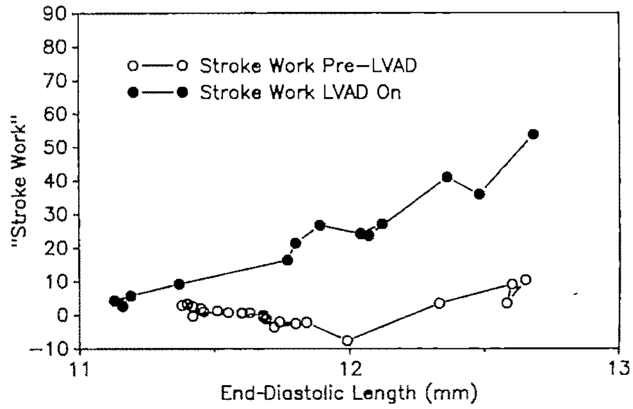

Fig 6. "Stroke work"–end-diastolic length relationship for a patient before and during support with the Novacor left ventricular assist device (LVAD).

ventricular support. In them, it rose just before support. In general, the patients who required the most pharmacological or mechanical support of the right ventricle were those with the largest hearts, as demonstrated by the end-diastolic and end-systolic volume indices. Group A_2 patients, however, also had large hearts but responded well to LVAS support. Examination of the total pulmonary artery resistances shows that in the group A_2 patients, total pulmonary resistance dropped and remained reduced while they were on the LVAS, whereas in the group B patients, total pulmonary resistance gradually increased by one hour of support.

In all but 2 of the patients surviving LVAS support, right ventricular dysfunction early in the support period could be managed pharmacologically. Each of these 2 patients had special problems. Patient 8 had severe adult respiratory distress syndrome and elevated intrapulmonary pressures. In patient 9, low peripheral resistance with coagulopathy developed and necessitated massive doses of vasoconstrictors and large amounts of volume transfusion, including 52 units of platelets, 37 units of packed red blood cells, and 18 units of cryoprecipitate. It was during these transfusions that a rise in pulmonary vascular resistance was accompanied by elevated right atrial pressure and right ventricular failure. In both of these patients, temporary right ventricular support was successful, and they were ultimately supported by the LVAS alone without the aid of inotropic agents.

The data obtained from sonomicrometry appeared to parallel the hemodynamic findings. The ejection-phase indices such as segmental power output and fractional fiber shortening mirrored the changes seen in RVEF. The greatest change in these indices was in the group A_2 patients, who also had the greatest percent increase in RVEFs. Also, these indices decreased in the group B patients, who showed a much smaller increase in RVEF. The smallest change occurred in those who required mechanical right ventricular support. Peak ventricular pressure tended to decrease, reflecting the afterload reduction afforded by the LVAS.

Finally, the end-diastolic length decreased in all but those patients who required mechanical right ventricular support and minimally in those requiring elevated pharmacological support. Before the LVAS is implanted, the segmental length–pressure loop has a characteristic isometric appearance because of an elevated afterload. Once the LVAS is turned on, the loop demonstrates more segmental excursion, less stasis at end-diastole, and a later peaking of ejection pressure. The characteristic "tail" at the end-diastolic, early-systolic portion of the loop may be attributed to geometric changes in the right ventricle such as early systolic leftward shift of the interventricular septum [24]. It is this change in the shape and increase in area within the pressure–length loop that results in an increase in the segmental power output after LVAS implantation. Although the inference of global change from segmental measurements is open to criticism, especially for the right ventricle [25], the data appear to correlate well with the hemodynamic data as well as with what is observed intraoperatively.

Because all of these measurements were dependent on right ventricular preload, the relationship of work to end-diastolic segmental length was examined. Before LVAS support, the relationship appears to be relatively flat, indicating little responsiveness of the right ventricle to preload. This suggests that this ventricle is working on the flat portion of the Frank-Starling curve. During LVAS support, the curve shows the ventricle to be much more responsive to preload. If the slopes of these curves can be taken to reflect the contractile state of the right ventricle, as they can for the left ventricle [26], the LVAS has allowed an increase in right ventricular contractility in the setting of reduced inotropic support. Further validation of these findings will have to be made under more controlled circumstances.

These findings are in keeping with those of Farrar and associates [27], who have shown that acute unloading of the left ventricle does not cause right ventricular failure. Rather, in patients with poor left ventricular function, it results in persistently improved right ventricular function, based on increased cardiac output. In these studies, the proposed mechanisms of the success of univentricular support could all play a role in the outcome for the patients in this trial. A leftward shift of the septum might allow better filling of the right ventricle through enhanced right ventricular diastolic compliance. The passive reduction of pulmonary artery pressure through reduction in left atrial pressure results in improvement in right ventricular function, which is very dependent on right ventricular afterload. In those patients with elevated pulmonary resistance, the increase in systemic output might have resulted in increased venous return and increased right ventricular volumes, thereby producing right heart failure. Finally, reduction in right ventricular transmural pressure might improve coronary blood flow to the right ventricular subendocardium and result in increased contractility.

In summary, this preliminary trial has shown that left ventricular support alone may be satisfactory for most chronically failing hearts. The clinical assessment of right ventricular failure can be misleading when the surgeon is attempting to decide whether to insert a univentricular or biventricular assist device or an artificial heart. In this series, patients with small right ventricular volumes and normal RVEFs did not show deterioration of right ventricular function while on the LVAS. Even patients with severely compromised right ventricles could be supported by a left ventricular assist device as long as pulmonary artery resistance did not rise during support. When right ventricular failure did occur, temporary mechanical right ventricular support resulted in recovery of function to the extent of allowing support to be continued with the LVAS alone.

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DISCUSSION

DR J. MICHAEL DUNCAN (Houston, TX): Dr Kormos and his colleagues at the University of Pittsburgh have presented a very interesting paper. They have reported a series of 11 patients, mortally ill from heart failure of diverse causes, requiring ventricular support with the Novacor pump while awaiting cardiac transplantation. Nine of these patients underwent successful transplantation, a truly remarkable accomplishment.

Our approach with these critically ill patients at the Texas Heart Institute is similar to that of Kormos and colleagues, namely, that heart failure can often be supported with left ventricular assistance alone, and that it is difficult to determine before LVAS implantation which patients will need additional right ventricular support.

Our experience has been with the Thermedics Heartmate left ventricular assist device, a pneumatically powered pump, and since 1986 we have used this device as a bridge to transplantation in 12 patients. Eight of these patients underwent successful transplantation, 1 died of donor heart failure, 2 died while on the device, and 1 is currently waiting for a transplant after being on the LVAS over 100 days. Two of these patients also required right ventricular assistance with the Bio-Medicus pump; 1 underwent successful transplantation and the other died of multisystem failure.

Early in our animal experience with the Thermedics device there was a long inflow conduit from the left ventricular apex to the pump, similar to the Novacor device. After explantation, we noted that a number of these conduits contained pannus formation, presumably as a result of low flow through this conduit. The design of the pump inlet was changed to eliminate this long inflow conduit.

In the manuscript that I had the privilege of reading before Dr Kormos' presentation, he indicated that in his series of patients there were eight thromboembolic events in 3 patients while on pump support. All of these events occurred at least 3 weeks after device implantation, when it is presumed that adequate anticoagulation was present.

I would like to ask Dr Kormos if they saw any evidence of pannus formation in the inlet conduits of the explanted devices, or if he has any explanation for the number of thromboembolic events.

The last 6 patients in our series have been anticoagulated with heparin or low molecular weight dextran in the early postoperative period, ie, the first four or five days, and then have been maintained with antiplatelet agents only. We have not encountered any thromboembolic events in our patients with over 550 implant days.

As we approach the time in the not too distant future when these devices will be implanted for permanent left ventricular assistance, it will be imperative that the pump utilized have a low incidence of thromboembolism, either with warfarin anticoagulation or antiplatelet agents.

Dr Kormos indicated that severe liver dysfunction is a contraindication to LVAS support. One of our patients had severe liver dysfunction before device implantation. After 37 days of LVAS support, his liver function studies returned to normal. He underwent transplantation and is now 17 months posttransplant.

What I am trying to show is that we are not always able to determine accurately from the laboratory studies which patients have reversible or irreversible organ dysfunction, and the approach should be, as Dr Kormos pointed out, to move ahead expeditiously with device implantation when there is a definite trend toward organ function deterioration.

Also, it is clear from our series that once an LVAS is implanted it is better to delay transplantation until renal, liver, and pulmonary functions have normalized. We like to have these patients off the ventilator, in good nutritional status, and ambulating, if possible.

I would like to ask Dr Kormos what their indications are regarding the timing of the transplantation in these patients.

DR FRANCIS ROBICSEK (Charlotte, NC): It was very interesting to hear Dr Kormos' comment, which I think is underlined by the well-known clinical fact we all know but seldom speak about: Many patients who are in biventricular failure and have normal pulmonary vascular resistance can be pulled through simply by insertion of an intraaortic balloon.

I would also like to mention Charlie Bailey's experiments in the very early 1950s in which he fibrillated dog hearts and inserted, I guess today you would call it an LVAS, a bypass pump from the left atrium to the aorta. The animals were kept alive for hours and hours and then successfully resuscitated. So this was really done in animal experiments 40 years ago, and it is very interesting to see that it now is applied clinically as well.

DR KORMOS: Dr Robicsek, indeed we recognize these early contributions and we are most impressed by the responsiveness of the right ventricle even when extremely impaired function is present.

Dr Duncan, I will address your two questions. First, with respect to thromboembolic episodes, 2 of the 3 patients who had thromboembolism had absolutely no modification of platelet function or any anticoagulation for four to five days after LVAS implantation. This was because of a substantial amount of postoperative bleeding. For this reason, our usual protocol of giving oral Persantine and dextran intravenously and/or heparin was violated. It is probably the first 24 hours after device implantation that is the most important for pacification of biomaterial surfaces. For that reason, all subsequent patients are started on Persantine and dextran early postoperatively and heparin or Coumadin is withheld until the patient's bleeding has stopped.

To address the second part of your question, on examination of the devices of these patients, we did not see pannus formation in the conduit itself, but we did see small amounts of fibrin and thrombus formation around the inlet valve stents similar to what you have described. We agree with your concept of the timing of transplantation in these patients and we also ensure that their condition is as stable as we can get it before transplantation. Specifically, we prefer to have as normal as possible liver and renal function and a stable pulmonary status, and in most cases, we like to have these patients transferred to a regular patient ward.

Management of Neonatal Critical Pulmonic Stenosis in the Balloon Valvotomy Era

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We evaluated our recent experience with management of neonatal critical pulmonic stenosis and intact ventricular septum between 1982 and 1988. Thirty-nine patients (aged less than 3 months) were treated initially by operation (group A, n = 19) or with balloon pulmonary valvotomy (group B, n = 20). Patients in group A were younger (5 ± 1.3 versus 18 ± 4 days in group B) (mean ± standard error of the mean) and had a greater degree of hypoxia (oxygen tension, 55 ± 4 versus 80 ± 6 mm Hg) ($p < 0.05$ for all variables). Ten patients in group A and 8 patients in group B had right ventricular hypoplasia, based on an angiographically determined index. Balloon pulmonary valvotomy was attempted in 20 patients at the time of the initial catheterization but was unsuccessful in 9 owing to inability to catheterize the hypoplastic right ventricular outflow tract (n = 8) and to recurrent infundibular stenosis (n = 1). Patients with failed balloon valvotomy were subsequently operated on within 24 hours. The early operative mortality (less than 30 days) was 25% (7 of 28); one death (9%) occurred after successful balloon valvotomy owing to associated critical aortic stenosis. The early postoperative gradient was 20 ± 2 mm Hg; the post-balloon valvotomy gradient was 18 ± 3 mm Hg. We conclude that balloon pulmonary valvotomy yields good results in patients with critical pulmonary stenosis with essentially normal-sized right ventricle, whereas surgical pulmonary valvotomy is required for patients with right ventricular hypoplasia.

(Ann Thorac Surg 1990;49:273–8)

Surgical treatment of critical pulmonary stenosis (PS) in the neonatal period is associated with a higher incidence of morbidity and mortality as compared with treatment of isolated PS in older infants and children [1, 2] despite improvements in surgical technique and perioperative care. Critical PS is commonly associated with underdevelopment of right-sided structures, including the tricuspid valve, right ventricular outflow tract (RVOT), and pulmonary artery [3]. The presence of a hypoplastic right ventricle has been identified as an important predictor of operative mortality [4].

Since balloon pulmonary valvotomy (BV) was introduced as a nonsurgical treatment for PS, many reports [5–7] have demonstrated the effectiveness of this procedure by showing an immediate decrease in the right ventricular–pulmonary artery systolic pressure gradient. However, the role of BV in the management of critical PS in the newborn period remains to be defined.

This study presents the immediate and intermediate-term results with BV and surgical treatment in patients with critical PS. Our results emphasize the importance of right ventricular size and morphology in determining the outcome with each of these therapeutic options.

Material and Methods

From 1982 to 1988, 39 patients (aged less than 3 months) with the diagnosis of critical PS and intact ventricular septum were treated at The Hospital for Sick Children, Toronto. All patients had situs solitus with concordant atrioventricular and ventriculoarterial connections. Patients with Ebstein's anomaly of the tricuspid valve were excluded. The diagnosis of critical PS was established angiographically by the presence of a fine jet of contrast media passing through a stenotic pulmonary valve (n = 37) or based on echocardiographic assessment (n = 2). The right ventricle/left ventricle peak systolic pressure was greater than 1 in 35 of 39 patients.

Since 1984, BV was usually attempted as the initial intervention regardless of right ventricular morphology, and the assignment to treatment, either BV or surgical valvotomy, was not intentionally randomized.

Nineteen patients underwent surgical valvotomy as the initial step in their management (group A). Twenty patients underwent BV at the time of the initial catheterization (group B). Balloon pulmonary valvotomy failed in 9 patients in this group, all of whom underwent subsequent operation within 24 hours.

The determination of right ventricular hypoplasia was based on the angiographic right ventricular index as suggested by Lewis and co-workers [8]. The right ventricular index was calculated by averaging the sum of biplane angiographic measurements of tricuspid valve annulus and of right ventricular inlet and outlet dimensions (at

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Table 1. Clinical and Hemodynamic Variables of Neonates With Critical Pulmonic Stenosis in the Surgical Group and Balloon Valvotomy Group[a]

Variable	Surgical Group	Balloon Valvotomy Group	*p* Value
No. of patients	19	20	
Age (days)	5 ± 1.3	18 ± 4	<0.05
Weight (kg)	3.3 ± 0.1	3 ± 0.2	
pH	7.34 ± 0.03 (7.26–7.41)	7.35 ± 0.03 (7.32–7.48)	
PO_2 (mm Hg)	55 ± 4	80 ± 6	<0.05
RV systolic pressure (mm Hg)	97 ± 4	88 ± 3.3	
RV/LV systolic pressure ratio	1.22	1.16	
RVEDP (mm Hg)	9.6 ± 0.4	8.4 ± 0.5	
RVEDP/LVEDP	1.4	1.2	
RVOT gradient[b] (mm Hg)	70 ± 3	68 + 2	

[a] Data are presented as mean ± standard error of the mean. [b] Only when the catheter entered the pulmonary artery or by Doppler echocardiography (group A, n = 16; group B, n = 14.)

LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PO_2 = partial pressure of oxygen; RV = right ventricular; RVEDP = right ventricular end-diastolic pressure; RVOT = right ventricular outflow tract.

end diastole) and relating this value to the aortic diameter at the diaphragm. The right ventricle was considered hypoplastic when the right ventricular index was greater than 11. The tricuspid valve was considered hypoplastic when the ratio of tricuspid annulus to the aortic diameter at the diaphragm was greater than 2 [9].

Surgical Procedures

Balloon atrial septostomy was performed at the time of cardiac catheterization in 10 patients. Prostaglandin E_1 administration was maintained perioperatively to keep the ductus arteriosus patent and improve oxygenation in 20 patients. Pulmonary valvotomy without cardiopulmonary bypass was performed in 21 patients: in 7 as an isolated procedure and in 14 in conjunction with a systemic–pulmonary shunt (modified Blalock-Taussig shunt in all). Pulmonary valvotomy was accomplished using a transventricular approach in 13 patients and a transarterial approach with normothermic inflow occlusion in 8 patients. Pulmonary valvotomy using cardiopulmonary bypass was performed in 7 patients, 5 of whom had transannular patch repair.

Balloon Valvotomy Procedure

The technique for BV has been described in detail previously [7]. Balloon catheters used in this procedure were approximately 120% of the diameter of the pulmonary valve annulus measured from a lateral right ventriculogram. Several balloon inflation-deflation cycles were performed until no waist caused by the stenotic pulmonary valve was visible during fluoroscopy. Right ventricular and pulmonary artery pressures were recorded before and immediately after the procedure, and angiography was repeated to confirm the adequacy of the opening.

Late Follow-up

Complete follow-up was obtained in both groups, including serial Doppler echocardiographic studies. Clinical status, the presence of residual pressure gradients across the RVOT, morphological abnormalities of the right-sided structures, and the need for reoperation were recorded for 26 ± 5 months (range, 2 to 60 months) in group A and for 19 ± 7 months (range, 5 to 44 months) in group B. All values are expressed as mean ± standard error of the mean. Unpaired and paired Student's *t* tests were used for comparison of continuous variables as necessary, and Fisher's exact test was used for discrete variables.

Results

Morphological Variables

Right ventricular hypoplasia was found in 10 patients (53%) in group A and in 8 (40%) in group B. Tricuspid insufficiency was graded as moderate to severe in 10 patients (52%) in group A and in 9 patients (45%) in group B. Combined valvular and infundibular stenosis occurred in 8 patients (42%) in group A and in 3 patients (15%) in group B. Pulmonary valve dysplasia was found in 3 patients (16%) in group A and in 3 (15%) in group B and was associated with small pulmonary valve annulus (less than 7 mm) in 3 patients (16%) in group A and 2 patients (10%) in group B.

Comparison of preoperative variables between the two groups is shown in Table 1. The patients in group A were younger ($p < 0.05$) and had a greater degree of hypoxemia ($p < 0.05$). The mean ratio of right ventricular to left ventricular peak systolic pressure was 1.2 in group A and 1.16 in group B. The right ventricular end-diastolic pressure was similarly high in both groups, reflecting a low compliance of the right ventricle. The preoperative RVOT pressure gradient was similar in both groups.

Balloon Valvotomy

Balloon pulmonary valvotomy was attempted in 20 patients with a success rate of 55% (11 patients) (Fig 1). Right ventricular hypoplasia was more common in patients who had unsuccessful BV (8 of 9 versus 0 of 11; $p < 0.001$) (Fig

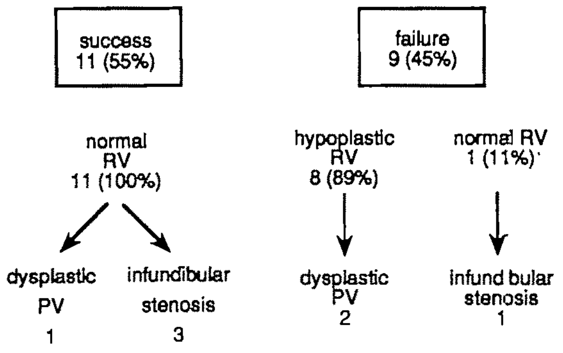

Fig 1. Results of balloon pulmonary valvotomy in 20 patients. (PV = *pulmonary valve;* RV = *right ventricle.)*

2). Failure resulted primarily from inability to advance a catheter across the hypoplastic infundibulum for placement of the balloon guidewire. Eight patients with failed BV were subsequently operated on, and 1 patient who had an immediate decrease in right ventricle–pulmonary artery peak systolic gradient from 85 to 35 mm Hg was operated on 12 days later owing to recurrence of the RVOT gradient as a result of fixed infundibular stenosis. The only death in group B occurred in a patient who had associated critical aortic stenosis and underwent a Konno operation after successful BV. Rupture of the right ventricular infundibulum occurred in 2 patients: 1 patient with a hemodynamically successful BV required only surgical control of the ruptured right ventricular infundibulum, and the second patient with hypoplastic right ventricle and dysplastic pulmonary valve in whom BV failed underwent surgical valvotomy followed by a systemic–pulmonary shunt. Two weeks postoperatively, however, a false aneurysm of the right ventricle developed, for which transannular patch reconstruction was performed (Fig 3). The mean right ventricle–pulmonary artery peak systolic gradient decreased from 68 ± 4 to 20 ± 4 mm Hg (range, 12 to 35 mm Hg) ($p < 0.01$) after BV, with a reduction in the right ventricular systolic pressure from 92 ± 4 to 47 ± 2.5 mm Hg ($p < 0.01$).

Surgical Valvotomy

The overall hospital mortality rate was 25% (7 of 28). Six of the 7 patients who died had moderate to severe right ventricular hypoplasia; the remaining patient had diffusely small pulmonary arteries with hypoplastic lungs confirmed at autopsy. A failed BV did not increase the risk of subsequent surgical valvotomy, as only 2 of 7 patients who died (28%) had unsuccessful BV before operation. Comparison of the different surgical approaches indicated a higher mortality (although not significantly different, $p = 0.2$) in patients who underwent valvotomy on bypass 43% (3 of 7) versus 19% (4 of 21) in patients who underwent closed pulmonary valvotomy with or without a systemic to pulmonary shunt (Table 2). The right ventricular systolic pressure decreased from 99 ± 3 mm Hg preoperatively to 40 ± 3 mm Hg ($p < 0.01$) postoperatively, and the transannular gradient decreased from 73 ± 2 to 18 ± 3 mm Hg (range, 0 to 38 mm Hg) ($p < 0.01$) (Fig 4).

Long-Term Follow-up

There was one late death (5%) among 21 survivors after surgical valvotomy and no late deaths after successful BV. Seven patients have required ten reoperations (Table 3). Systemic pulmonary shunts were performed ten days (n = 1) and 6 weeks (n = 2) after transventricular valvotomy because of persistent cyanosis. A Glenn shunt, tricuspid annuloplasty, and atrial septal defect closure was performed in 1 patient, and ligation of a Blalock-Taussig shunt was performed because of development of congestive heart failure in 2 patients. Three other patients underwent transannular patch insertion at 2 weeks, and at 8 and 18 months after transarterial pulmonary valvotomy and Blalock-Taussig shunt as a result of recurrent infundibular and valvular stenosis (n = 2) or false aneurysm of the right ventricle (n = 1). One of these patients, in whom severe pulmonary insufficiency and intractable congestive heart failure developed, subsequently underwent unsuccessful pulmonary valve replacement.

Survivors in both groups are uniformly asymptomatic. Repeated Doppler echocardiography performed every 6 months after operation or BV demonstrated only a mild tricuspid insufficiency in 3 patients in group A, as well as a variable degree of pulmonary insufficiency and growth of the hypoplastic right ventricle. The mean transannular pressure gradient had not changed significantly in either group A or group B at the time of the most recent follow-up.

Comment

The results of this study unequivocally indicate that the criteria for selecting neonates with critical PS for either surgical treatment or BV should be based on right ventricular morphology. In our experience, BV uniformly failed in neonates having right ventricular hypoplasia as defined by an objective angiographic index. On the other hand, BV was successful in patients with a well-developed right ventricle and in a small subset of patients with associated infundibular stenosis.

Similar results were reported recently by Zeevi and associates [10]. Failure to cross the pulmonary valve in 1 patient was attributed to a hypoplastic right ventricle; dilation of the pulmonary valve was successful in 5 patients with a right ventricle of normal size.

The operative mortality in neonates and infants undergoing operation for critical PS has varied in previous reports between 3.4% and 26% [1, 2]. Right ventricular hypoplasia has been identified previously as a risk factor after closed pulmonary valvotomy [4]. In our experience, right ventricular hypoplasia was present in 64% of patients managed surgically. Other investigators [3, 11] have reported an incidence of right ventricular hypoplasia ranging from 5% to 68%. The relatively high incidence of right ventricular hypoplasia in patients treated surgically in the present series may reflect preferential application of BV to patients with a well-developed right ventricle.

The early postoperative Doppler studies demonstrated substantial relief of the RVOT gradients. This finding, as well as evidence of right ventricular growth on the late echocardiographic studies, suggests a surgical approach

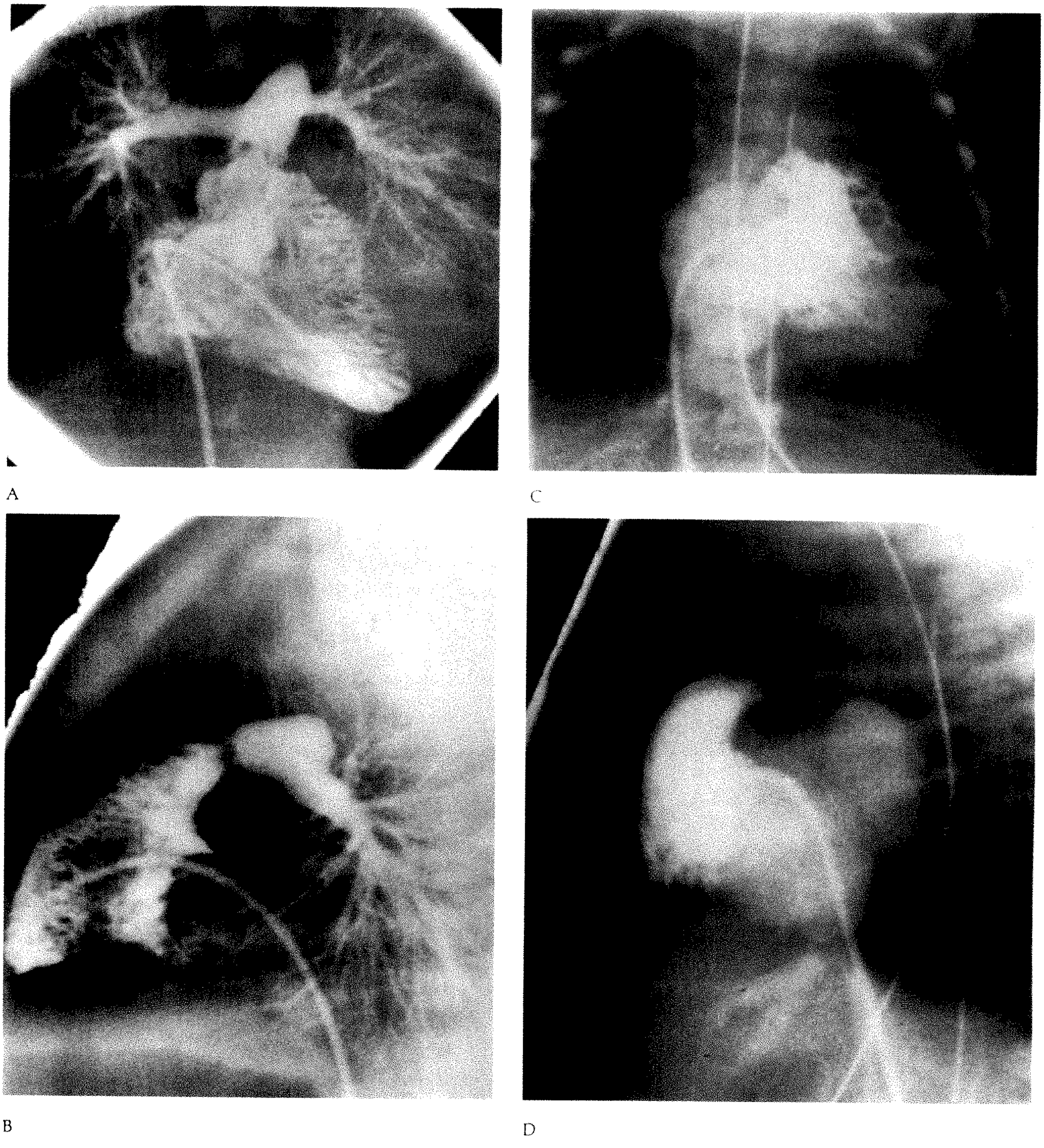

Fig 2. Axial frontal (A) and lateral (B) right ventriculogram in diastole in a patient with successful balloon pulmonary valvotomy (3 weeks old) show right ventricular hypertrophy with a normal triscuspid valve and thickened doming pulmonary valve. Frontal (C) and lateral (D) right ventriculogram in diastole in a newborn with failed balloon pulmonary valvotomy show a small right ventricular cavity, a small regurgitant tricuspid valve, and very little forward flow through the pulmonary valve.

consisting of pulmonary valvotomy with a Blalock-Taussig shunt without the need for primary transannular patch repair on bypass. This is in agreement with other reports [2, 3, 12] that have shown that critical PS can be treated successfully with transventricular or transarterial approaches and less successfully with transannular patch or valvotomy using cardiopulmonary bypass [13]. On the other hand, De Moor and colleagues [14] demonstrated that transannular outflow patch is a safe procedure for neonates with critical PS and hypoplastic right ventricle, with an early survival rate of 87% (7 of 8 patients).

The systemic to pulmonary shunt is particularly important for patients with associated infundibular stenosis and provides an important source of pulmonary blood flow

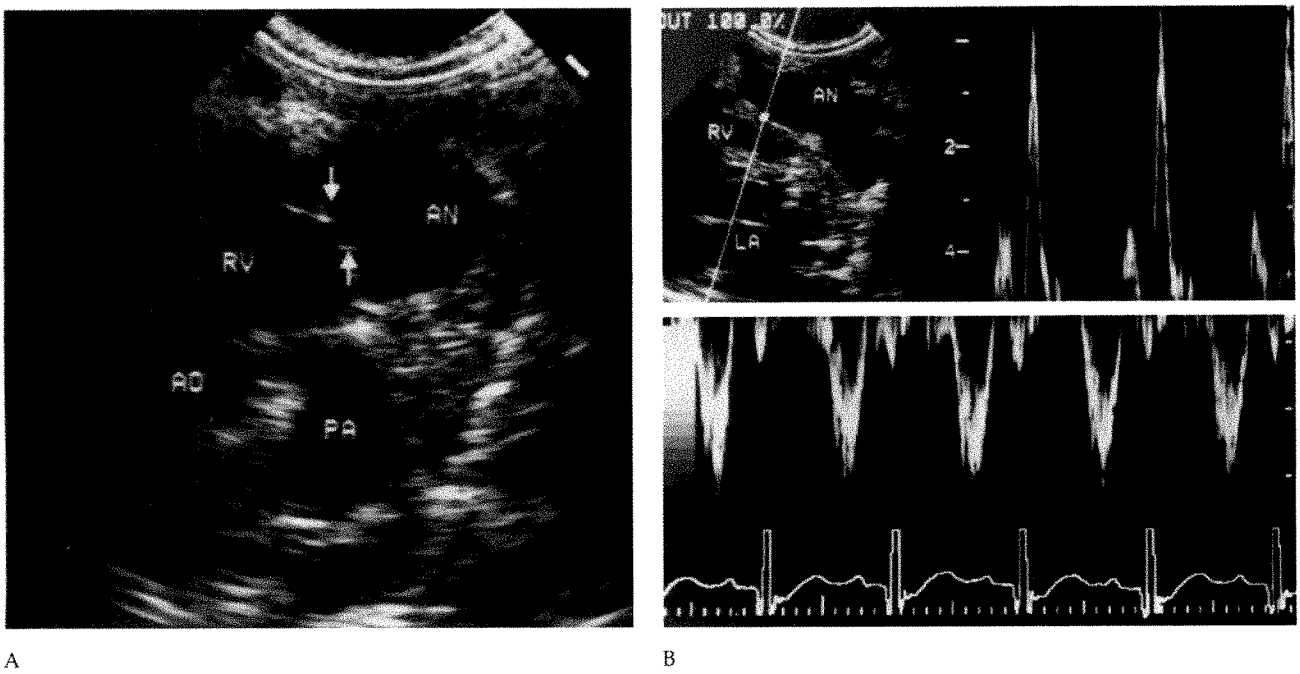

Fig 3. (A) Doppler echocardiography demonstrates false aneurysm (AN) *of the right ventricle* (RV) *which developed after failed balloon pulmonary valvotomy.* White arrows *point to site of rupture. (B) The Doppler sample volume situated at the entry site into the aneurysm shows systolic and diastolic shunting from the right ventricle into the aneurysm.* (AO = *aorta;* LA = *left atrium;* PA = *pulmonary artery.)*

pending regression of the dynamic RVOT obstruction and improvement in right ventricular compliance, a finding observed in a previous analysis of our earlier experience with critical PS [15]. Only 2 patients (1 with a dysplastic pulmonary valve) had high RVOT pressure gradients in the intermediate follow-up that necessitated later transannular patch insertion. We [7] and other investigators [16] have noted regression of infundibular hypertrophy after successful BV as well as after surgical valvotomy [17, 18], suggesting that there is no need for muscle resection at the initial procedure.

The angiographic findings of severely thickened and immobile valve leaflets represent a neonatal expression of the dysplastic pulmonary valve and occurred in 15% of patients (6 of 39) in this series. Closed pulmonary valvotomy in this subset of patients yielded results similar to those obtained in the overall group. Balloon pulmonary valvotomy was successful in 1 of 2 patients. Two of 5 hospital survivors required reoperation for residual valvular stenosis, consistent with the relatively high incidence of recurrent stenosis reported in older infants with a dysplastic pulmonary valve treated by isolated pulmonary valvotomy [19, 20].

The late results for patients successfully managed in the newborn period by either surgical treatment or BV continue to be favorable with regard to functional capacity, right ventricular growth, and tricuspid valve function.

Table 2. Surgical Valvotomy Results

Treatment group	No. of Patients	No. of Deaths (%)
Valvotomy without CPB	21	4 (19)
Alone	7	2 (33)
Plus shunt	14	2 (14)
With CPB	7	3 (43)
Valvotomy	2	1 (50)
Transannular patch	5	2 (40)
All patients	28	7 (25)

CPB = cardiopulmonary bypass.

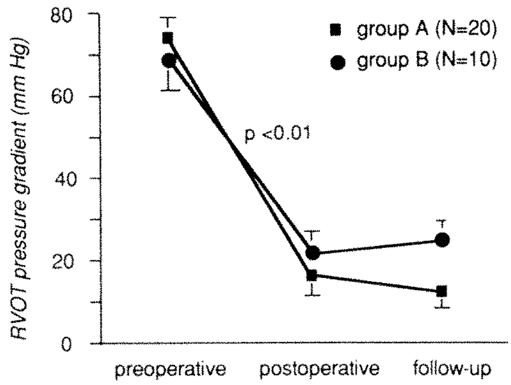

Fig 4. Comparison of preoperative and postoperative right ventricular outflow tract (RVOT) *pressure gradients in group A (including 5 patients with failed balloon pulmonary valvotomy) and before and after balloon pulmonary valvotomy in group B, and gradients during follow-up.*

Table 3. Reoperations in 7 Patients

Operation	No.
Central shunt	1
Transannular patch	3
Pulmonary valve replacement	1
Glenn, tricuspid annuloplasty; ASD closure	1
BT shunt	2
Ligation of BT shunt	2
Total	10

ASD = atrial septal defect; BT = Blalock-Taussig.

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DISCUSSION

DR ALDO R. CASTANEDA (Boston, MA): I was surprised to learn how dissimilar our experiences at the Children's Hospital in Boston are relating to this specific disease entity with the experience of Dr Caspi and associates.

Over the last 4 years, Dr Lock and his colleagues succeeded in 19 of 20 neonates to successfully dilate the stenotic pulmonary valve. This was accomplished without early or late mortality. Only 1 of the 20 patients later required a patch plasty because of a hypoplastic pulmonary valve annulus. Also, 40% of those 20 patients had a hypoplastic right ventricle, 60% had tricuspid regurgitation, and 20% had right ventricular sinusoids.

Thus, our experience does not support the notion that right ventricular size or the presence of tricuspid regurgitation affects survival in this disease. This clearly contrasts with our data on congenital aortic stenosis, in which left ventricular size is the major determinant of survival, or with pulmonary atresia and intact ventricular septum, in which right ventricular-dependent coronary circulation seems to be one of the major risk factors.

Therefore, based on our experience, we continue to favor percutaneous BV over surgical valvotomy, including in the critically ill neonate, with or without hypoplastic right ventricle. I do not know the reason for this difference in results; perhaps it is operator-dependent. Dr Caspi might want to comment on that issue.

DR CASPI: I am not sure I have a good answer for the difference between the results at Boston Children's Hospital and our results. However, as I mentioned before, BV failed almost uniformly in all our patients with moderate to severe right ventricular hypoplasia. Furthermore, two complications that occurred, I think, present the side effects of this procedure in those critically ill patients.

Reduction of Complement Activation During Bypass by Prime Manipulation

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Complement activation is believed to be of importance in the development of complications arising after cardiopulmonary bypass. The effect on complement activation of priming the extracorporeal circuit with crystalloid alone, crystalloid plus albumin, or crystalloid plus the plasma expander polygeline was assessed in 36 patients undergoing coronary artery operations with cardiopulmonary bypass using a bubble oxygenator. Activation of the alternative and common complement pathways was monitored before, during, and after the bypass period by measuring concentrations of factor B and its fragment Ba and C3 and its fragment C3d. Complement activation occurred in all three groups of patients, with no difference between the crystalloid and crystalloid-albumin groups. In contrast, Ba fragment concentrations were persistently and significantly lower during and after bypass in the polygeline group, denoting reduced complement activation. C3d levels also showed a tendency to be lower in this group. Our results indicate that addition of polygeline to the priming solution reduces complement activation. Because complement activation is associated with morbidity after cardiopulmonary bypass, addition of polygeline to the priming solution may offer an inexpensive method of reducing morbidity after cardiopulmonary bypass.

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Cardiopulmonary bypass (CPB) activates the complement system, producing a variety of split products potentially damaging to the patient [1, 2]. Because the extent of complement activation during CPB can be correlated to the risk of postoperative morbidity, efforts to reduce activation are of potential clinical importance [3]. Previous studies have evaluated the effects of different oxygenator types [4–7], perioperative steroid administration [7, 8], anticomplement agents [9], and exclusion of the oxygenator from the extracorporeal circuit [10] on reducing complement activation.

The composition of the solution used to prime the extracorporeal circuit may influence complement activation. In one study [11], no evidence of complement activation was found in 55% patients during CPB when using a circuit prime containing the plasma expander polygeline (Haemacell; Behring, Marburg, FRG). Whereas most studies have failed to demonstrate a difference in complement activation when comparing bubble and membrane oxygenators during CPB [4–6], Cavarocchi and co-workers [7] reported significantly less activation in the membrane group. In that report, however, half of the patients in the membrane group underwent CPB with a prime containing 12.5% vol/vol 5% albumin. Cavarocchi and co-workers did not comment on the possible effects of the addition of albumin to the circuit prime.

We undertook a prospective study of the effects of three different priming solutions (crystalloid alone, crystalloid-albumin, and crystalloid-polygeline) on complement activation during CPB. The components of the common pathway (C3) and the alternative pathway (factor B), and their split products (C3d and Ba) were measured serially throughout the study period.

Material and Methods

Thirty five male patients and 1 female patient undergoing elective coronary artery operations were included in the study. No patients received steroids or nonautologous blood transfusion before or during the study. Cardiopulmonary bypass using a Harvey 1700 bubble oxygenator was accomplished in all patients using right atrial drainage and ascending aortic return. Cardioplegic arrest was used for myocardial protection. Patients were randomly allocated on a purely rotational basis to one of the three prime groups (group 1, 2,000 mL of Hartmann's solution; group 2, 1,600 mL of Hartmann's solution plus 400 mL of 4.5% albumin solution; group 3, 1,500 mL of Hartmann's solution plus 500 mL of polygeline).

Blood samples were drawn from the arterial catheter at the following times: (1) at anesthesia induction; (2) after heparizination (2 mg/kg); (3) at 90 seconds, (4) 10 minutes, (5) 30 minutes, and (6) 60 minutes after institution of bypass; (7) at the end of bypass; (8) at 5 minutes, (9) 15 minutes, and (10) 30 minutes after administration of protamine (2 mg/mg of administered heparin); and (11) at 2 hours after patients had returned to the intensive care unit. After collection, blood samples were kept on ice until sampling was complete. Plasma was then separated and stored at −70°C for subsequent batch analysis.

Complement indexes of the parent molecules C3 and factor B and their fragments C3d and Ba were measured.

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Table 1. Patient Ages and Cross-Clamp and Perfusion Times

Variable	Group 1	Group 2	Group 3
Age (yr)	56.5 (9.7)[a]	56.2 (19.3)	54.9 (6.0)
Cross-clamp time (min)	46.3 (16.9)	49.0 (25.2)	49.2 (16.7)
Perfusion time (min)	80.7 (29.1)	79.2 (37.0)	83.2 (23.3)

[a] Values in parentheses are standard deviations.

Concentrations of C3 and factor B were measured by laser nephelometry using specific antisera (Behring, Marburg, FRG; Dako, Copenhagen, Denmark). Concentrations of split products C3d and Ba fragment were assayed by sensitive nephelometric techniques using specific antisera after differential polyethylene glycol precipitation as described previously [12, 13]. The assay results for parent molecules and split products were corrected for hemodilution. Statistical comparison within groups was made by paired *t* test, and comparison between groups at each sampling time was made using the Mann-Whitney U test. All complement assays were performed in a single-blind manner.

Results

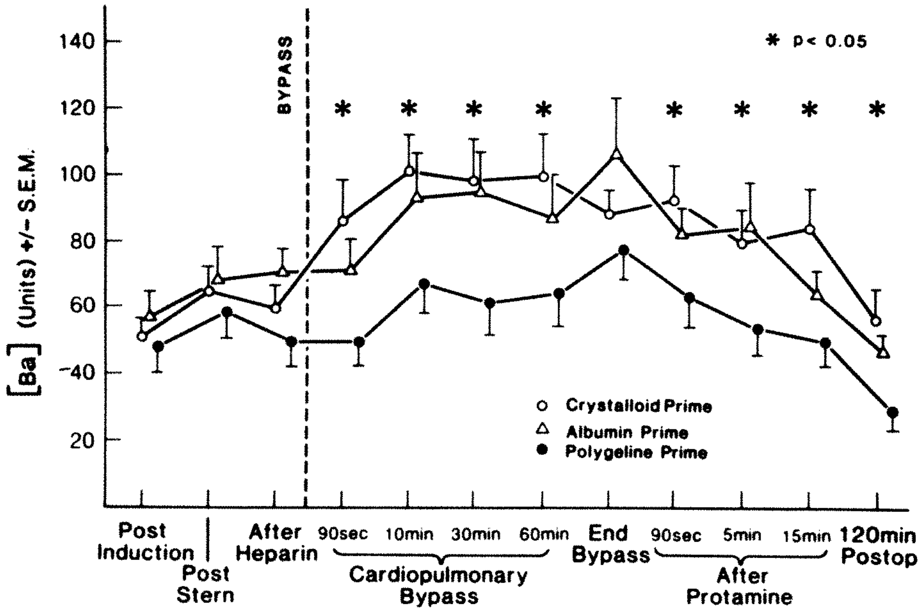
Patient ages, cross-clamp times, and perfusion time were well matched between groups (Table 1). No patient required additional heparin or nonautologous blood transfusion during the study. Intraoperative monitoring of electrolytes and acid-base status revealed no significant difference between the groups. Postoperatively, 1 patient in both groups 1 and 3 required reexploration for bleeding. No difference in postoperative morbidity was apparent between groups, and times to extubation were similar.

Ba fragment levels rose significantly during CPB in all groups ($p < 0.05$) but were persistently and significantly lower in group 3 at all sampling points during and after CPB ($p < 0.05$) (Fig 1). C3d levels increased steadily and significantly during CPB in all groups ($p < 0.05$), with levels in group 3 tending to be lower than in other groups although the differences between groups did not reach statistical significance (Fig 2). Neither Ba fragment nor C3d levels increased significantly compared with end-bypass values after administration of protamine (Figs 1, 2). Concentrations of factor B decreased significantly within 10 minutes of initiation of CPB in all groups ($p < 0.05$), but no difference was detectable between groups at any point before, during, or after CPB (Fig 3). Similar but not significant changes were observed in the concentration of C3, levels remaining persistently low until two hours after operation (Fig 4).

Comment

The present study identifies prime manipulation with the plasma expander polygeline as a possible method of reducing complement activation during bypass. Alternative pathway activation as manifested by Ba fragment production was persistently and significantly lower in the polygeline group although decreasing factor B levels indicated that it was not abolished completely. Complement activation during CPB is probably initiated through the alternative pathway by the polymers of the extracorporeal circuit, with subsequent activation of C3, the pivotal point of the classic, alternative, and common pathway [14]. C3 conversion was also reduced in the polygeline group, although not to a significant extent. This limited decrease in common pathway activation probably reflects the "cascading" nature of the complement system, whereby a single activated molecule is capable of activating a large number of subsequent molecules in the cascade. C3d is a degradation fragment of C3b produced by a series of enzymatic reactions occurring after activation of C3 by classic or alternative pathway C3

*Fig 1. Ba fragment levels during study (units per milliliter); *p value less than 0.05 (Mann-Whitney test) for polygeline group values versus other groups.*



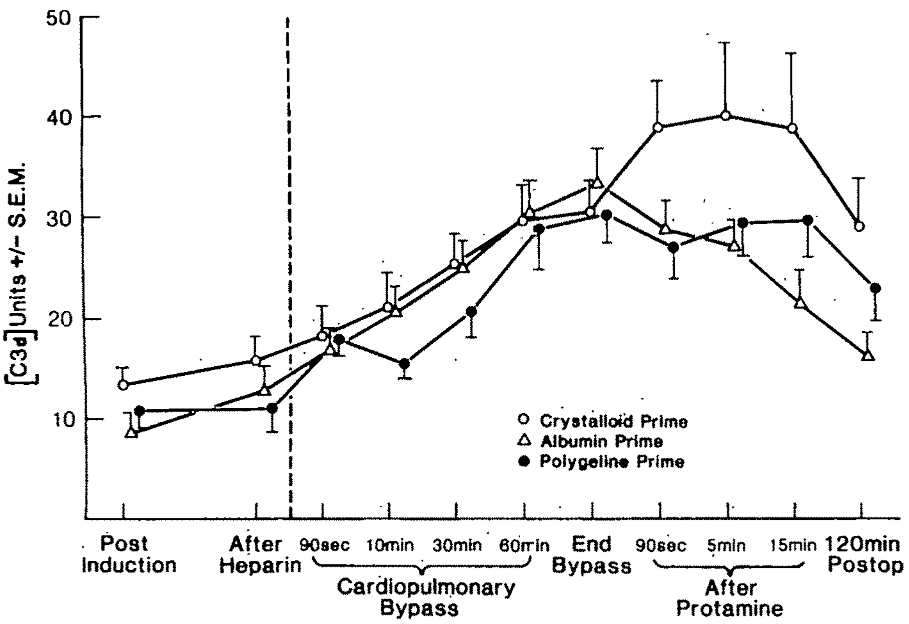


Fig 2. C3d levels during study (units per milliliter). In all groups, significant elevation occurred within 10 minutes of initiation of cardiopulmonary bypass.

convertases, and whether polygeline is capable of interfering with these processes in vitro is not known.

Ba fragment levels decreased in all groups after discontinuation of CPB, and this decrease was not affected by administration of protamine. This is consistent with the pathway of complement activation by heparin–protamine interaction occurring through the classic and not the alternative pathway [15]. In contrast to previous studies that identified a secondary peak of complement activation (indicated by C3a production) after protamine administration [15, 16], we did not observe a similar increase in C3d production after administration of protamine.

Reduction of complement activation during CPB is of immediate clinical relevance because decreasing complement activation during CPB would probably result in a reduction of postoperative morbidity [3]. This is suggested by the known pathophysiological effects of activated complement fragments, the correlation of extent of complement activation during CPB with the risk of postoperative morbidity [3], and the demonstration of elevated levels of complement fragments in patients in whom adult respiratory distress syndrome develops after CPB [17]. In this study, in common with other small group studies [15, 16], discernible differences in morbidity between groups were not observed. Larger series with more sensitive indexes of morbidity are required to investigate the relationship further.

The mechanism by which polygeline reduces alternative pathway activation is not clear, but may result from binding of the gelatin to potential complement-activating

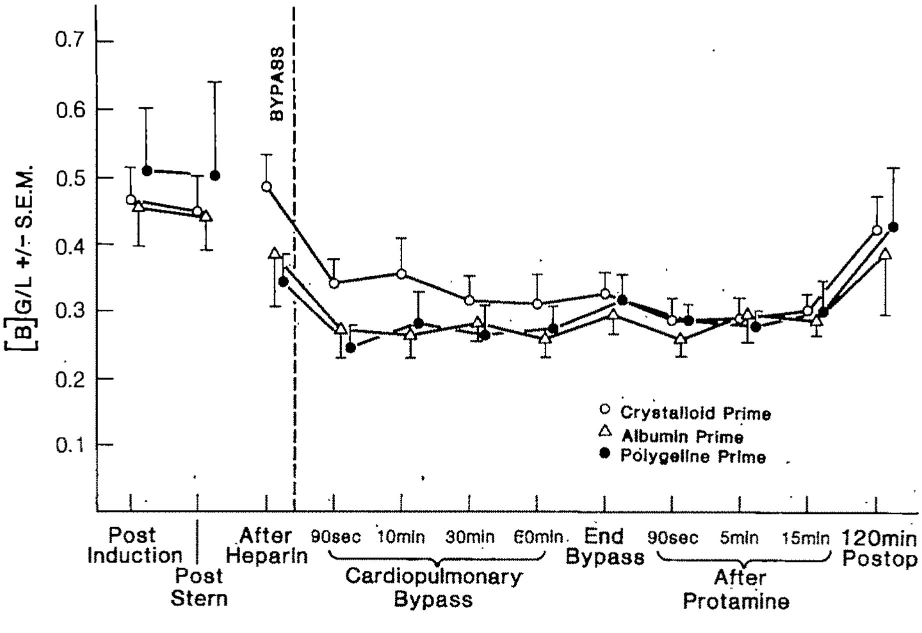


Fig 3. Factor B concentrations during cardiopulmonary bypass. Significant reductions occurred within ten minutes of cardiopulmonary bypass.

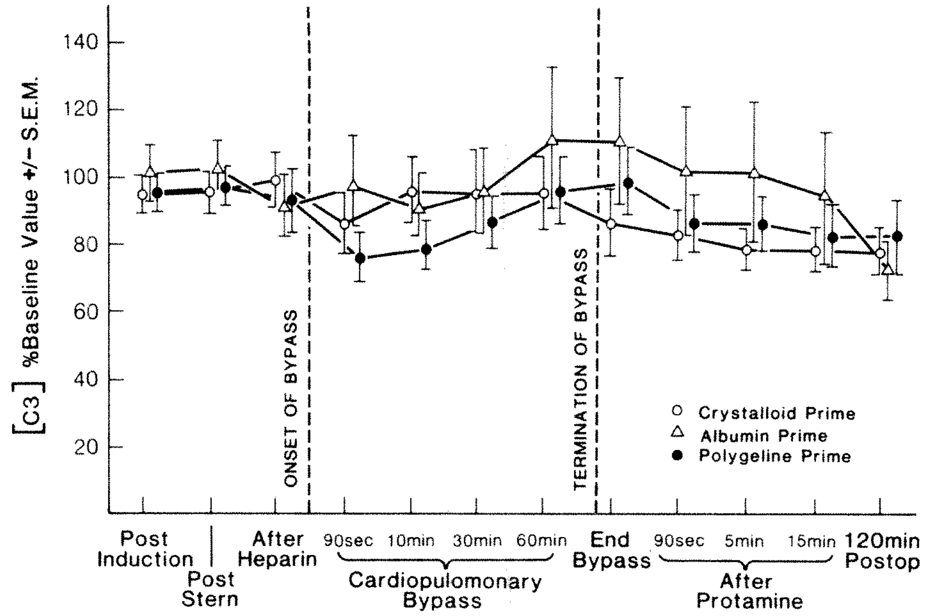


Fig 4. C3 concentrations during cardiopulmonary bypass. Significant changes in C3 concentration did not occur during cardiopulmonary bypass in any group.

sites within the polymers of the oxygenator and extracorporeal circuit. This may in turn protect parent molecules in blood from exposure and activation during CPB. The failure to detect complement activation during CPB in other studies using polygeline in the prime supports this assumption. Selective binding of Ba fragment to polygeline that prevents polyethylene glycol solubilization and assay is a second less likely possibility but is consistent with our inability to detect a decrease in factor B consumption. Clearly, further in vitro studies are required to investigate the effects of possible prime additives on blood–polymer interactions and complement assay techniques. As no benefit was demonstrated in the albumin group, changes in oncotic pressure or buffering capacity of the prime are unlikely to be responsible for these observations.

Polygeline is a urea-linked gelatin, available as a plasma expander, that has been used as a component of the circuit prime for CPB in varying concentrations and shown to be safe and effective as a hemodiluting agent [18, 19]. Whether higher concentrations than those used in the present investigation would reduce complement activation further requires additional study. If a causal relationship between complement activation by the extracorporeal circuit and postoperative morbidity is clearly proved, our results suggest that manipulation of prime constituents would offer an inexpensive method to reduce such morbidity without the attendant risks of steroids or left heart cannulation in double-reservoir bypass techniques [10].

Supported by Grant No. 86/7 from the Clinical Research Committee, National Heart and Chest Hospitals.

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Important Notice From the American Board of Thoracic Surgery Regarding Approved Training

The American Board of Thoracic Surgery will no longer accept training in thoracic surgery obtained in residency programs that are not approved by the Residency Review Committee for Thoracic Surgery of the Accreditation Council for Graduate Medical Education. This policy will apply to residents initiating training after July 1, 1990. Notification of this policy has been sent to all program directors. If you wish to obtain further information, please contact the Board office.

Esophageal Carcinoma in Young Patients

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The clinicopathological features of esophageal carcinoma were examined from the viewpoint of age differences in a study of 364 consecutively treated patients. The three groups studied were: group I, aged less than 49 years; group II, aged between 50 and 69 years; and group III, aged more than 70 years. There were no significant differences among the three groups with regard to sex ratio, site and length of the lesion, gross types, histological grade, depth of tumor invasion, vessel permeation, lymph node metastasis, TNM classification, incidence of incomplete resection, or crude actuarial 5-year survival curves. The malignant potentiality of the esophageal carcinoma in young patients did not differ from that in older patients in terms of deoxyribonucleic acid distribution pattern. The only difference clearly evident between young and older patients was the number of hospital deaths due to complications: That of the young patients was significantly lower than that of the older patients ($p < 0.05$). Esophageal carcinoma in persons aged less than 50 years appeared to behave biologically like the same neoplasm in older people, whereas gastric and colorectal carcinomas behave differently in various age groups.

(Ann Thorac Surg 1990;49:284–6)

Carcinoma of the esophagus occurs mainly in the sixth, seventh, and eighth decades of life and is rare in patients aged less than 50 years. There are reports of clinicopathological differences in gastric [1–3] and colorectal [4–6] carcinomas between the young and the elderly. Few data are available on clinicopathological findings of young patients with esophageal carcinoma, however. We report our observations of 364 patients who underwent operation to remove a malignant lesion of the esophagus, especially from the viewpoint of age differences.

Material and Methods

From 1965 to 1988, 364 Japanese patients with esophageal carcinoma were treated surgically in our institution. The age distribution is shown in Figure 1. Three groups were studied: group I included 28 patients aged less than 49 years at first diagnosis; group II included 254 patients aged 50 to 69 years; and group III comprised 82 patients aged more than 70 years.

All records for each patient were reviewed with regard to location of the carcinoma, length and radiographic type of carcinoma seen on the barium study, preoperative adjuvant therapy, TNM classification [7], incidence of radical and palliative operations, postoperative complications, cause of death and hospital mortality, and 5-year survival. All patients were followed for 5 years or to the end of the study period. Survival curves were calculated using the Kaplan-Meier procedure [8], and all data relating to the long-term results were analyzed using the generalized Wilcoxon test.

Macroscopic and microscopic evaluations were made according to rules established by the Japanese Society for Esophageal Diseases [9]. An analysis of the deoxyribonucleic acid (DNA) content in the malignant cells was made of 182 cases, using the two-wavelength method described elsewhere [10]. For statistical analysis of the clinicopathological data, the χ^2 test and Student's t test were used.

Results

Male preponderance was evident in all three groups. There was no difference in preoperative therapy among the three groups. The midesophagus was the area most commonly affected, and the ulcerative type was common to each group. There were no differences regarding site of

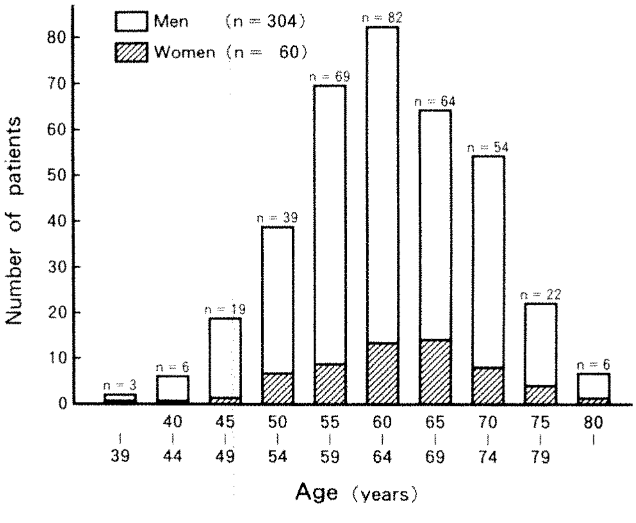

Fig 1. Age distribution of patients with esophageal carcinoma.

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Table 1. Clinical Data[a]

Variable	Group I (<49 yr, n = 28)	Group II (50–69 yr, n = 254)	Group III (>70 yr, n = 82)
Sex (M/F)	86/14	83/17	84/16
Site of carcinoma			
Cervical esophagus	4	5	4
Thoracic esophagus			
Upper	7	12	5
Mid	60	59	66
Lower	29	24	25
Esophagogram			
Protruded	25	19	23
Superficial	11	6	7
Ulcerative	64	75	70
Length of tumor in esophagogram (cm), mean ± SD	6.73 ± 3.54	6.47 ± 2.54	6.11 ± 2.56

[a] Data are given in percentages.

lesion, radiographic type, or tumor length, as seen on the esophagograms (Table 1).

Table 2 compares histological features of the tumors. There were no significant differences among the three groups with regard to histological type, depth of tumor invasion, vessel invasion, lymph node metastasis, TNM classification, or DNA distribution pattern.

Table 2. Histological Features[a]

Variable	Group I (<49 yr)	Group II (50–69 yr)	Group III (>70 yr)
Histological types	n = 28	n = 248	n = 81
Well-differentiated SCC	14	23	28
Moderately differentiated SCC	50	48	40
Poorly differentiated SCC	29	25	25
Other[b]	7	4	7
Tumor invasion into adventitia	n = 28	n = 254	n = 82
No invasion	32	24	24
Invasion positive	29	43	43
Invasion into neighboring tissue	39	33	33
Vessel invasion	n = 27	n = 243	n = 78
Lymphatic			
Yes	56	55	56
No	44	45	44
Vascular			
Yes	30	23	27
No	70	77	73
Lymph node metastasis	n = 28	n = 254	n = 82
Yes	57	55	55
No	43	45	45
TNM classification	n = 28	n = 254	n = 82
I	14	8	10
IIA	25	26	20
IIB	4	7	5
III	32	39	45
IV	25	20	20
DNA distribution pattern	n = 14	n = 125	n = 43
I	0	1	0
II	21	22	16
III	29	42	47
IV	50	35	37

[a] Data are given in percentages. [b] Esophageal carcinomas other than SCC including adenocarcinomas, adenosquamous carcinomas, undifferentiated carcinomas, and mucoepidermoid carcinomas.

SCC = squamous cell carcinoma.

Data on resectability, postoperative complications, and mortality and cause of death are summarized in Table 3. Resectability did not differ among the three groups, and the frequency of postoperative complications was much the same among the three groups. In group I, 19 of 28 patients had incomplete resections; ten were the result of direct invasion to the trachea, bronchus, or aorta, and the other nine were the result of residual metastatic lymph nodes that could not be excised. The number of younger patients (group I) who died in the hospital with complications excluding recurrence of esophageal carcinoma was significantly low as compared with the number of older patients (group III) ($p < 0.05$).

The 5-year actuarial survival curves for the three groups of patients are shown in Figure 2. There was no significant difference among the three groups.

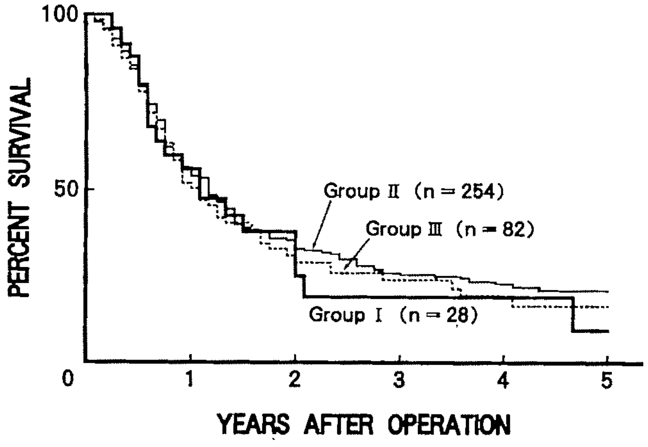

Fig 2. Survival curves of patients with esophageal cancer (%). One-year, 3-year, and 5-year survival rates are: 56.1%, 19.0%, and 9.5%, respectively, in group I; 54%, 26.3%, and 21.6%, respectively, in group II; and 50.7%, 24.4%, and 16.7%, respectively, in group III.

Comment

Although gastric [1–3] or colorectal carcinomas often occur in patients in the second and third decades of life [5, 6, 11], esophageal carcinoma is rare in these age groups. We classified young patients with esophageal carcinoma as those aged less than 49 years. Young patients with gastric or colorectal carcinomas have been reported to be aged less than 30 [3], 35 [1, 2], or 40 [5, 6] years.

Table 3. Postoperative Data[a]

Variable	Group I (<49 yr, n = 28)	Group II (50–69 yr, n = 254)	Group III (>70 yr, n = 82)
Resectability			
Complete resection	32	46	45
Incomplete resection	68	54	55
Complications			
No	54	54	43
Yes	46	46	57
Lung	21	22	34
Anastomotic leakage	11	12	15
Death within 30 days after operation	0	5	11
Hospital death due to complications[b]	4[c]	9[c]	20
Within 30 days	0	5[c]	11
>30 days	4	5	9
Cause of death			
Pneumonia	4	4	12
Anastomotic leakage	0	2	1

[a] Data are shown in percentages. [b] Hospital death due to esophageal carcinoma excluded. [c] Significance: $p < 0.05$ versus group III.

Gastric carcinoma in the young differs from that which occurs in older patients, especially with regard to pathological features: poorly differentiated or diffuse-type carcinomas predominate histologically, infiltrative type is rather frequent even on gross inspection, intestinal metaplasia is less frequent, and gastritis occurs less commonly than in older patients [1–3]. The usual sex ratio is altered, with a preponderance [3] or equivalence [1, 2] of women among younger patients and a consistent preponderance of men among older patients. Most young patients are in a clinically advanced stage, and the prognosis is poor [1–3].

Colorectal carcinoma in the young also has features different from those of older patients. The predominant histological type of colorectal tumor in young patients is mucinous or poorly differentiated adenocarcinoma, with a clinically more aggressive nature and a predisposition to early metastasis [5, 6]. In addition, delayed diagnosis in young patients can lead to a relatively poor prognosis [5, 6].

In the current study of younger patients with esophageal carcinoma treated in our clinics, the pathological features such as histological differentiation, vessel invasion, and lymph node involvement showed no definite characteristics as compared with findings in older patients. The cytophotometric DNA pattern of esophageal carcinoma clearly defined the malignant potential [10]. We [12] used a multivariate approach to assess the prognosis of patients with esophageal carcinoma and concluded that the DNA pattern appears to be an independent prognostic indicator. The ratio of favorable (types I and II) to unfavorable (types III and IV) DNA patterns in young patients did not differ significantly from findings in older patients. The pathological and DNA cytophotometric analysis in the current study suggests that the malignant potential of esophageal carcinoma in young patients does not differ from that in older patients.

The survival rate of young patients with esophageal carcinoma did not differ from that of older patients. The only difference was that the rate of hospital death due to complications in the young was significantly low compared with rates in older patients. In conclusion, esophageal carcinoma in persons aged less than 50 years appears to behave biologically like other neoplasms that occur in older people, whereas gastric and colorectal carcinomas behave differently in various age groups.

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Use of the Argon Beam Electrocoagulator for Performing Pulmonary Wedge Resections

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The argon beam electrocoagulator (ABC) is a new form of electrocautery that is thought to be more effective than standard electrocautery. It has been used primarily in procedures associated with major blood loss such as liver transplantation and laparotomy for trauma. It has not been used in thoracic operations. We evaluated the safety and efficacy of the argon beam electrocoagulator for performing pulmonary wedge resections in an animal model by comparing it with standard electrocautery and suture closure. Variables used to compare the three methods of resection included perioperative blood loss, duration of chest tube air leak, and depth of necrosis and severity of inflammatory reaction in the lung at ten days and 3 weeks after resection. The argon beam electrocoagulator was as effective as standard electrocautery and suture closure in controlling air leaks, and caused less acute tissue injury than standard electrocautery. The argon beam electrocoagulator provides a safe and effective method for performing small pulmonary wedge resections, and should be evaluated in the clinical setting for this purpose.

(Ann Thorac Surg 1990;49:287–91)

The argon beam electrocoagulator (ABC) is a new form of electrocautery that is thought to be more effective than standard electrocautery. The ABC looks similar to a standard cautery machine but functions in a very different manner. It emits a jet of argon gas, which clears blood away from the area being cauterized, and simultaneously conducts radio-frequency energy of uniform intensity and depth to the target area without actually coming in contact with it. This provides very rapid hemostasis while producing minimal eschar [1]. As a result, the ABC is now used in operations such as liver resections in which it is critical to control bleeding from large, open surfaces quickly and efficiently.

The ABC has not been used in thoracic surgery, although it has obvious potential applications in procedures such as decortication or major chest wall resection in which bleeding from large, raw surfaces is sometimes a problem. We thought the ABC might also be useful in performing multiple pulmonary wedge resections as, for instance, in patients being operated on for pulmonary metastases. If it were effective in providing hemostasis and sealing air leaks, it could preserve pulmonary parenchyma by obviating the need to reapproximate the edges of resected lung with staples or sutures.

Because there was no information about the safety of the ABC for doing pulmonary wedge resections, we decided to evaluate it in an animal model by documenting its ability to control air leaks and provide hemostasis, and by examining the pathological extent of injury that it produces in lung tissue.

Material and Methods

Studies were performed with 24 New Zealand white rabbits weighing 3.8 to 5.4 kg (mean weight, 4.6 kg). Institutional guidelines for the care and use of laboratory animals were adhered to throughout the experiment. The rabbits were randomly assigned to three groups of 8 animals each, according to the way in which pulmonary wedge resection was to be performed: group A (ABC), group B (standard electrocautery), and group C (suture closure). The animals were anesthetized with intramuscular administration of a solution (0.7 mL/kg) that contained ketamine (50 mg/mL), xylazine (7.14 mg/mL), and atropine (0.045 mg/mL). After orotracheal intubation, the animals were mechanically ventilated at an inspired oxygen fraction of 1.0, a tidal volume of 20 mL/kg, and a respiratory rate of 16 breaths per minute. Anesthesia was maintained with 1% to 1.5% halothane.

Under sterile conditions, a left lateral thoracotomy was performed in the fifth intercostal space. A vascular clamp was gently applied to the left upper lobe, thereby isolating a section of lung measuring at least 3 × 4 cm. A wedge resection was performed by amputating the portion of lung distal to the clamp with scissors. The resected lung was submitted for pathological examination after being fixed in the inflated state with formalin.

With the vascular clamp still loosely applied to the lung, the bleeding, raw surface of pulmonary parenchyma along the area of resection was then managed in one of three ways: (1) cautery with the ABC (Bard Electro Medical Systems, Englewood, CO) using a power setting of 60 W; (2) cautery with standard electrocautery (Valley Lab SSE2-K; Valley Lab, Boulder, CO); and (3) 5-0 Prolene suture closure using the traditional method of a running horizontal mattress stitch followed by a continuous suture

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in an over-and-over manner. The vascular clamp was then removed. A 16F chest tube was inserted through a separate inferior stab wound and positioned up to the apex of the pleural space. The chest tube was attached to a pleural drainage container (Atrium 2002; Atrium Medical Corp, Hollis, NH) and placed to −20 cm H_2O of suction. The thoracotomy was closed, and the animals were awakened from anesthesia and extubated.

Fluid output and air leak from the chest tube were recorded every ten minutes. The chest tube was removed when there was no evidence of bleeding or air leak for a minimum of ten minutes. The rabbits were returned to their cages and were given routine feeding and care. Chloramphenicol, 50 mg/kg subcutaneously, was administered at the start of the experiment and 24 hours after operation as routine perioperative antibiotic coverage. Buprenorphine (Buprenex, Norwich Eaton Pharmaceuticals, Norwich, NY), 0.0125 mg/kg intramuscularly, was given at the end of the operation and as necessary postoperatively for analgesia.

In each group, 3 rabbits were killed seven to ten days postoperatively ("early" animals). The remaining 5 rabbits in each group were killed 20 to 24 days postoperatively ("late" animals). The left thoracotomy was reopened immediately after the animal was killed, and the left lung was removed. The lung was submitted for pathological examination after being inflated and fixed in formalin. Two to five histological sections taken perpendicular to the lung surface and incorporating the area of the wedge resection were prepared from each specimen.

The wedge resection specimens submitted at the time of operation were examined for any underlying inflammation or lung disease. After the animal was killed, the healing lung biopsy site was evaluated and graded according to the following variables: (1) depth of necrosis, (2) depth of granulation tissue, (3) type and degree of inflammation, and (4) presence of other pathological processes. Depth of necrosis (thickness of eschar) and thickness of the injured zone were measured at approximately 0.5-mm intervals on each histological section using a videomicroscope connected to a quantitative image-analysis system. The latter consists of a Matrox PIP-640B frame grabber board (Dorval, Que, Canada) connected to a DOS-based microcomputer controlled by OPTIMAS image-analysis software (Bioscan, Edmonds, WA). Final image magnification was 66-fold. The mean and standard error of the mean were calculated for the three largest measurements from each section. The results shown are the data for the section from each animal with the thickest zone of injury.

Inflammation was assessed qualitatively as to type of inflammatory cells and overall intensity. All of the measurements and histological evaluations were done by one pathologist (R.S.), who was blind as to the way the resections had been performed.

Data were analyzed by Student's t test for unpaired data to compare group A with groups B and C with respect to amount of blood loss and duration of air leak, depth of necrosis, and depth of granulation tissue in early and late animals. Differences were considered significant if the value of p was less than 0.05.

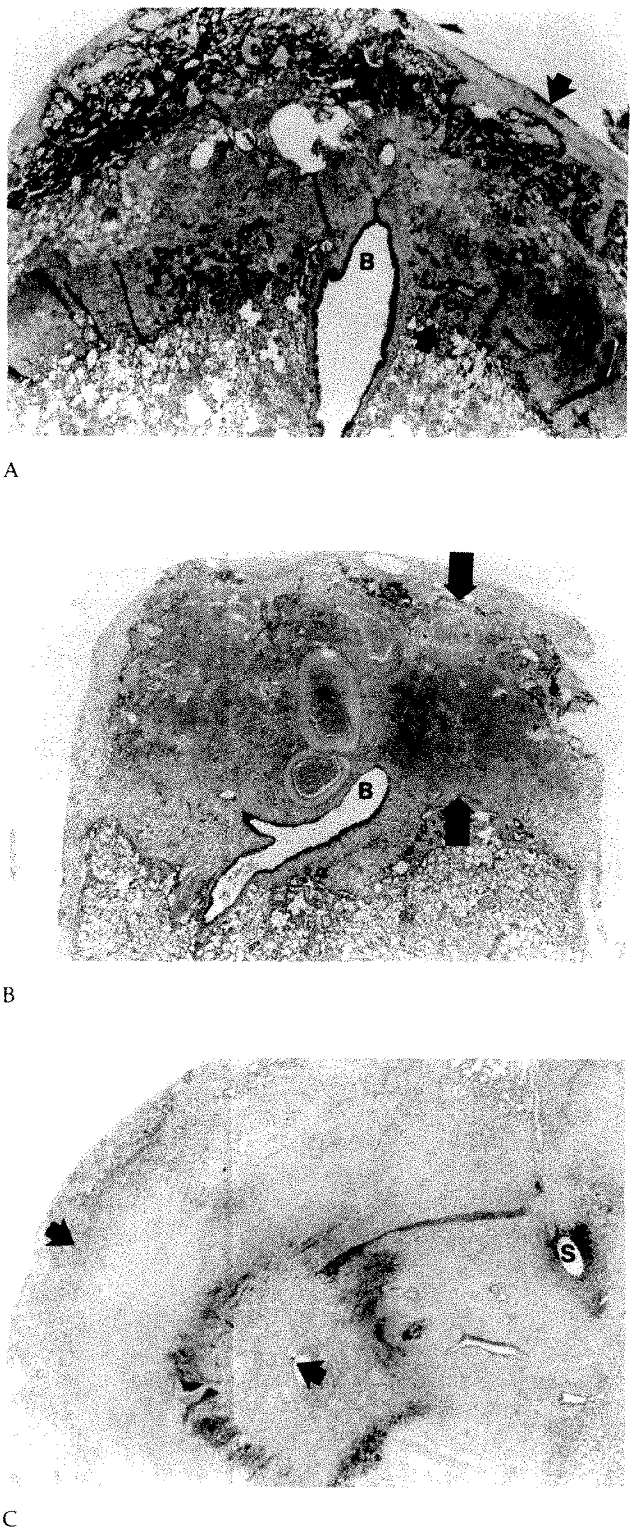

Fig 1. Comparison of tissue injury at ten days after pulmonary wedge resection. Lungs managed with (A) the argon beam coagulator and (B) standard electrocautery show a well-defined, continuous eschar of coagulated lung tissue and subjacent band of granulation tissue (area between arrows). *Coagulated arteries (A) and bronchioles (B) are seen within the eschar. In contrast, (C) lungs managed with suture closure show localized concentric zones of necrosis* (area between arrows) *surrounding sutures (S). (All hematoxylin and eosin, ×66 before 50% reduction.)*

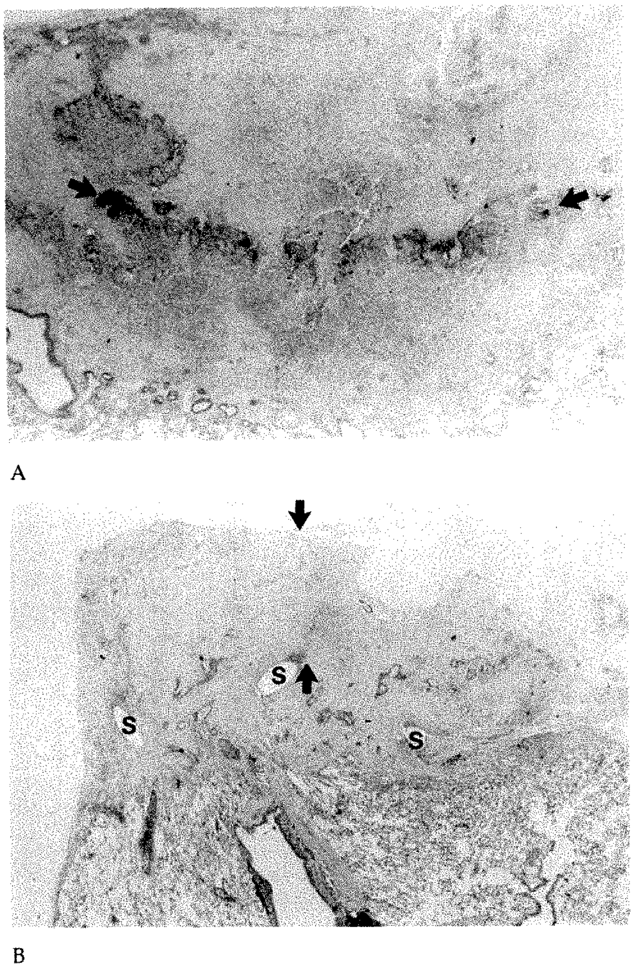

Fig 2. Comparison of tissue injury at 21 days after pulmonary wedge resection. (A) Lungs managed with standard electrocautery show a narrow zone of residual eschar (area between arrows) *bounded on either side by thick bands of granulation tissue. Lungs managed with the argon beam coagulator have a similar appearance. (B) Sutured lungs show mostly fibrosis* (area between arrows) *surrounding sutures* (S) *with little residual inflammation. (Both hematoxylin and eosin, ×66 before 50% reduction.)*

Results

In group A, there were 3 animals in the early group and 5 in the late group. At the recommendation of the veterinarian, 1 rabbit in group B and 2 rabbits in group C were electively killed early because of failure to thrive. Thus, group B had 4 animals in both the early and late groups, and group C had 5 animals in the early group and 3 in the late group. The mean interval between operation and death for the early and late groups, respectively, were as follows: nine days and 20 days in group A; 8.7 days and 20.3 days in group B; and 7.8 days and 24 days in group C.

The mean duration of chest tube air leak was 2.5 ± 1.3 minutes in group A compared with 16.9 ± 4.8 minutes in group B ($p = 0.021$) and 11.3 ± 4.0 minutes in group C ($p = 0.071$). There was no measurable blood loss in any of the three groups.

Evaluation of the initial lung biopsy specimens showed that only 1 animal had major underlying lung disease. This animal, a member of group C, had moderate to severe interstitial pneumonitis. Postoperatively, this animal appeared ill and was killed after seven days. Patchy necrotizing bronchopneumonia was present at the time of death. This animal was excluded from the analysis of pathological changes seen after wedge resection.

The histopathological reaction to injury was qualitatively similar for groups A and B. In the early animals, there was a well-defined, continuous, and homogeneous eschar of coagulative necrosis that covered the area of previous biopsy (Figs 1A, B). This was sharply demarcated from subjacent lung tissue by a distinct band of granulation tissue 0.5 mm thick. A thin band of proliferating pleura was found intermittently on the surface of the eschar. Moderate numbers of chronic inflammatory cells were present in the granulation tissue zone in both groups. Small collections of polymorphonuclear cells and a few multinucleated giant cells were present in or near the eschar.

In the late animals, an exuberant foreign-body giant cell reaction was present that was directed at residual coagulated tissue. Much of the original eschar was now converted to fibrous granulation tissue (Fig 2A). Moderate numbers of chronic inflammatory cells persisted in the granulation tissue. Pleural adhesions were found in both groups.

Sutured lungs had a distinctly different appearance from lungs treated with either the ABC or standard electrocautery. In early animals, the inflammatory reaction and zones of ischemic necrosis were discontinuous and confined to the areas of tissue surrounding the suture material (Fig 1C). The ischemic zone was demarcated from surrounding lung by a narrow band of granulation tissue. Moderate numbers of chronic inflammatory cells and occasional polymorphonuclear cells were present, but there were few giant cells. The pleura and subpleural alveoli were viable. In contrast to cauterized lungs in the late animals, which still showed exuberant granulation tissue with inflammation, sutured lungs in the late animals demonstrated replacement of necrotic tissue by minimally inflamed fibrous tissue (Fig 2B).

Measurements of the depth of necrosis and of granulation tissue seen in early and late animals, respectively, are shown in Table 1. The discontinuous nature of the tissue

Table 1. Depth of Lung Tissue Injury in Animals Undergoing Pulmonary Wedge Resection

Variable	Argon Beam Electrocoagulator	Standard Electrocautery	*p* Value
Depth of necrosis	2.03 ± 0.09	4.10 ± 0.07	0.015
(mm): "early"	2.36 ± 0.08	3.41 ± 0.04	
animals	2.18 ± 0.17	3.35 ± 0.04	
		2.98 ± 0.12	
Depth of	2.77 ± 0.25	3.80 ± 0.50	0.06
granulation tissue	3.58 ± 0.14	3.75 ± 0.30	
(mm): "late"	3.71 ± 0.11	3.59 ± 0.05	
animals	2.99 ± 0.38	2.01 ± 0.43[a]	
	2.93 ± 0.32		

[a] This specimen could not be evaluated because of partial slough of eschar.

reaction in group C made it difficult to compare it with groups A and B. Comparison of the maximal depths of necrosis in group A and group B early animals, however, showed that the mean in group A (2.19 ± 0.095 mm) was significantly less than in group B (3.46 ± 0.23 mm) (p = 0.015). The eschars in group A were of more uniform thickness (range, 2.03 to 2.36 mm) than in group B (range, 2.98 to 4.10 mm). At 3 weeks, the difference in thickness of injured lung tissue between groups A and B was only marginally significant (p = 0.06). In the sutured lungs of group C, the zones of ischemic necrosis at ten days ranged from 2.59 to 4.23 mm. At 3 weeks, the areas of fibrosis ranged in depth from 1.57 to 3.84 mm.

Comment

Electrocautery has been an integral part of surgical technique since the 1920s when it was developed by William T. Bovie, a professor of electrical engineering at the Massachusetts Institute of Technology, and introduced into clinical use by Harvey Cushing. Electrocautery represented a major advance in coagulation capability over simple thermal cautery, which had been in use until that time. Electrocautery is based on a radio-frequency current that generates individual "arc tunnels" into the tissue. As the cautery process progresses, the individual arc tunnels interconnect, forming a reticular or sponge-like structure in the treated tissue. It is this reticulum that provides faster and more effective coagulation than thermal cautery [1].

The ABC represents a technological improvement in electrocautery. This device uses a gentle flow of inert, nonflammable argon gas, instead of the conventional medium of air, to conduct radio-frequency current to the target tissue. The argon gas also blows blood away from the target tissue, thus allowing more efficient cauterization. The ABC functions in a noncontact manner. The handpiece incorporates a sensor that automatically initiates the electrical current only when the tip of the handpiece is within 1 cm of the target tissue. The ABC is thought to produce a more homogeneous eschar and to be more effective than standard electrocautery because it distributes the arc tunnels in a more even pattern and more uniform depth to the target tissue. In addition, the temperature in the tissue being cauterized never exceeds 110°C, both because of a cooling effect of the argon gas and because no further conduction of radio-frequency energy into tissue occurs once eschar forms. This is thought to minimize tissue destruction and necrosis [2].

The ABC is increasingly popular in operations associated with substantial blood loss from large, open surfaces. These procedures include liver resection, liver transplantation, and laparotomy for splenic or renal trauma. It has also been used in head and neck operations, and in gynecological operations to debulk ovarian cancer from vascular areas in the abdomen [3–6]. In thoracic procedures such as pleurectomy, redo thoracotomy, and major chest wall resection, the ABC could provide the optimal method of hemostasis.

We were interested in whether the ABC would control blood loss and air leaks from the raw surface of pulmonary parenchyma. This is not usually an issue in lobectomies, but can be a problem in procedures such as segmentectomies, multiple wedge resections, and decortication. Traditionally, blood loss and air leaks have been controlled with staples, sutures, electrocautery, or a combination of these [7, 8]. Both staples and suture closure can result in sacrifice of a substantial amount of lung tissue. This is a particular concern in patients who have limited lung function or who are undergoing multiple resections for pulmonary metastases [9, 10]. A highly effective form of electrocautery might allow coring out of pulmonary metastases and obviate the need for staples or sutures, thereby preserving lung tissue. Our data indicate that the ABC is as effective as standard electrocautery or suture closure in controlling blood loss from the raw lung surface. The ABC controlled air leaks better than standard electrocautery and at least as well as suture closure.

We were especially interested in determining the amount of tissue destruction that the ABC produced in lung tissue because there has been no documentation of this. A power setting of 60 W was chosen because this is in the range of what has been used in other soft-tissue applications. The ABC was compared with standard electrocautery and with suture closure because these are two techniques commonly used for the resection of small areas of lung. Staples were not used because we thought that rabbit lungs might not be of adequate thickness to allow proper application of the staplers used in humans. The 5-0 Prolene suture was selected for suture closure because of its nonreactivity and because it seemed less likely than Dexon or Vicryl to tear the very fragile lung of rabbits. Animals were killed seven to ten days after wedge resection to assess pathological changes at a point when necrosis and inflammatory reaction were likely to be well established, and at 20 to 24 days after resection when the inflammatory reaction was expected to be largely resolved and healing ongoing. Both forms of cautery produced coagulative necrosis of alveolar lung tissue, but the measured depth of necrosis and granulation tissue in the early animals was significantly less in the lungs cauterized with the ABC compared with standard electrocautery. This suggests that the acute tissue destruction caused by the ABC may be more superficial than that caused by standard electrocautery or suture closure. The differences in extent of tissue injury between the two groups treated with cautery became less distinct with time, however. By qualitative assessment, resolution of tissue injury and complete healing appeared to occur sooner with suture closure than with either form of cautery.

In summary, the ABC seems effective in controlling blood loss and in sealing air leaks from small areas of raw pulmonary parenchyma. It causes a different pattern of tissue injury and results in less complete healing at 3 weeks than does suture closure. However, it causes less immediate tissue injury and no more late tissue destruction than does standard electrocautery. Our experience in an animal model suggests that the ABC is safe for performing wedge resections and managing open areas of pulmonary parenchyma and that it should be evaluated clinically for this purpose.

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Vascular Properties of Canine Lungs Perfused With Eurocollins Solution and Prostacyclin

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Although Eurocollins solution (ECS) is commonly used for lung preservation, its vascular effects and their time course and response to pharmocological interventions are not well understood. The effect of 4°C ECS on the pulmonary circulation was assessed in excised canine left lower lobes. The roles of static oxygen inflation and prostacyclin infusion during ECS perfusion were also examined. The lobes were divided into five groups: time control (A), ECS with oxygen (B), ECS without oxygen (C), ECS with glycine buffer (D), and ECS with prostacyclin (E); group D was the control for E. Eurocollins solution had no effect on gas exchange but had a marked effect on the pulmonary circulation. Vascular conductance decreased from 22.6 to 18.9 mL/min/cm H_2O and from 21.3 to 14.1 mL/min/cm H_2O with average vascular closure increasing by 1.2 and 2.1 cm H_2O in groups B and C, respectively. The decreased vascular conductance and increased vascular closure was associated with a reduction in vascular compliance from 1.63 to 1.25 mL/cm H_2O. When prostacyclin was added to ECS, the reduction in vascular closure was much less and was associated with a decrease in vascular closure and no loss of vascular compliance. Eurocollins solution increases pressure cost for perfusion by causing both vascular obstruction and increased tone, especially when oxygen is not provided. This is significantly overcome by addition of prostacyclin infusion during ECS perfusion.

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Currently, lung preservation methods for transplantation allow only four hours from the time of removal to implantation despite many efforts to extend this period [1–3]. The most widely used approach is flushing with cold Eurocollins solution (ECS), followed by hypothermic storage. Eurocollins solution is a hyperosmolar electrolyte solution rich in potassium and phosphate. Its composition and hypothermia combine to decrease metabolism to a minimum, thereby preventing ischemic injury. Concerns about acute increases in pulmonary vascular resistance after lung transplantation [4, 5] have led to use of potent vasodilators such as prostaglandin E_1 and prostacyclin (PGI_2) [6, 7] as adjuvants to ECS.

The present report describes a method used to study systematically the pulmonary vascular effects of combined ECS perfusion and PGI_2 infusion and demonstrate its efficacy. Prostacyclin has two known effects on the pulmonary circulation that theoretically could prove beneficial in this setting. It is a very potent vasodilator of the pulmonary circulation and also strongly inhibits adenosine diphosphate-induced platelet aggregation. The role of static oxygen inflation during ECS perfusion was also examined. This could have important implications for lung preservation, as oxygen radicals have been implicated in lung injury; investigators have also shown that statically inflated lungs continue to consume oxygen at temperatures as low as 6°C and may therefore require oxygen [8].

Material and Methods

Animal and Lobar Preparation

Thirty-three healthy mongrel dogs weighing between 16 and 32 kg were anesthetized with pentobarbital sodium (30 mg/kg), intubated, and ventilated with a small animal respirator. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). The basic preparation has been previously described in detail [9]. A left thoracotomy was performed, heparin was administered, and the left lower lobe artery, vein, and bronchus were cannulated. After the animals were exsanguinated, the lobe was excised and suspended from a force transducer for continuous monitoring of lobar weight changes in the range of 100 mg. Arterial and venous cannulas were connected to constant level reservoirs of adjustable height, and inflow (Pi) and outflow (Po) pressures were continuously monitored using the hilum as the zero reference point. The bronchial cannula was connected to a 100% oxygen source and airway pressure (Pa) was continuously measured. The blood was pumped by a roller pump from the outflow reservoir through a heat exchanger, filter, inflow reservoir, and flow meter. A third reservoir was used for ECS perfusion and PGI_2 infusion, with additional tubing to divert the flow of ECS coming out of the lobe. The experimental preparation is shown in Figure 1.

Protocol 1

In the first series of 19 lobes, the pulmonary vascular effects of ECS with and without oxygen were studied. Inflow pressure, Po, and Pa were set in such a way that

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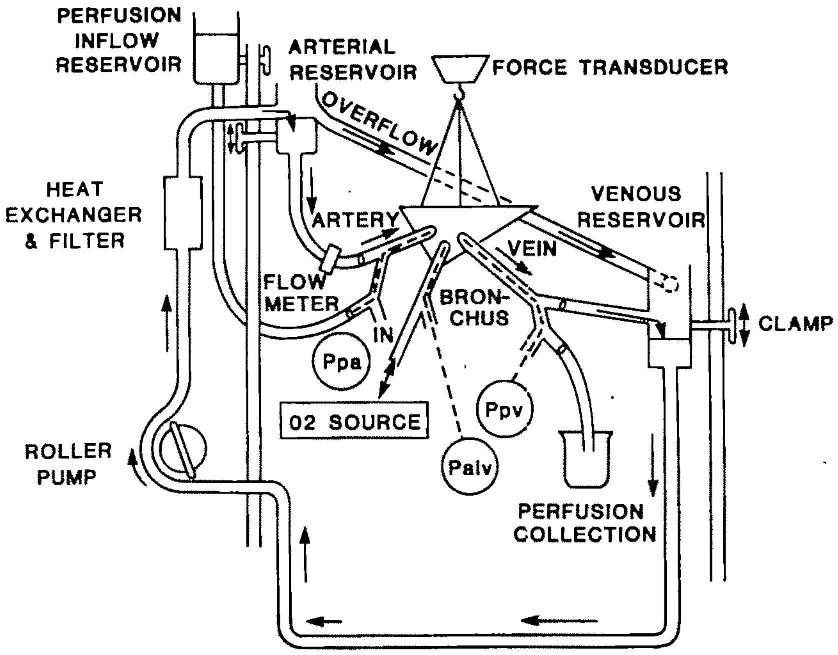

Fig 1. Isolated lobe preparation. Canine left lower lobes were suspended from a force transducer for continuous monitoring of total lobar weight. Blood flows by gravity from the arterial reservoir through a flow meter into a venous reservoir, from which it is pumped by means of a roller pump through a filter and heat exchanger back into the arterial reservoir. Flow, inflow, outflow, and airway pressures were measured continuously. Inflow and outflow pressures are altered by adjusting the height of their respective constant level reservoirs. The perfusion inflow reservoir connected by means of a Y-connector and stopcock to the inflow tubing. The perfusate was diverted into a beaker through a Y-connector and stopcock.

the entire lobe was in a zone 3 of West and colleagues [10] with Pa of 5 cm H_2O, Po of 14 cm H_2O, and initial Pi of approximately 18 cm H_2O. After stabilization, defined as weight gain of less than 100 mg over 1 minute, the initial wet weight of the lobe and its connections was determined. By raising the inflow reservoir and increasing Pi in a series of small increments, flow was altered and the pressure flow characteristics of the lobar circulation were determined. Due to resistance in the outflow tubing, this sometimes resulted in a slight change in Po, and the outflow reservoir was then adjusted to maintain Po at 14 cm H_2O. Inflow and outflow pH, oxygen and carbon dioxide tensions, and hematocrit were measured.

The lobes were then randomized into three groups. Group A was a control group in which the procedure was repeated as described after 45 minutes had elapsed. This was the average time required for ECS perfusion and rewarming in groups B and C. The ECS had previously been chilled to 4°C and filtered to remove any undissolved crystalline material. In group B, the flow of oxygen was continued while 1.25 to 2 L of ECS was infused; we attempted to achieve a perfusion time of approximately 15 minutes. The temperatures of the ECS and the effluent were measured. In group C, the flow of oxygen was interrupted for the duration of the ECS perfusion, resulting in near-total atelectasis. Thereafter, blood flow was resumed, and the lobes were flushed with approximately 100 mL of blood to remove residual ECS. The flow of oxygen was resumed for group C, and the lobes were rewarmed and allowed to stabilize. Pressure flow curves, levels of blood gases, and hematocrit were again measured as described. The lobe with and without its connections was weighed to obtain the final wet weight. Dry oxygen was blown through the lobe for 24 hours, followed by further drying in an oven to constant weight to obtain the dry weight.

Protocol 2

In the second series of 14 lobes, the effect of adding PGI_2 to ECS perfusion was studied. Canine pulmonary vasodilation with systemic infusion rates ranging from 20 to 1,000 ng/kg/min has been reported [11]. Because the average wet weight of a lobe is about 100 g, an infusion rate of 20 ng/min was chosen. The protocol was much the same as that followed for group B. with two changes. Through a side port in the inflow tubing either glycine buffer (group D) or PGI_2 with glycine buffer (group E) was infused in a random fashion. Because PGI_2 requires preparation in an alkaline solution, a separate control was required for group E. In both groups, the infusion was started approximately four minutes before and continued for approximately three minutes after completion of ECS perfusion. A fixed volume of 2 L of ECS was perfused; this resulted in slightly longer perfusion times than in the previous series.

In addition to the measurements in protocol 1 in this series of experiments, pressure flow in zone 2 and a pressure volume profile of the lobar circulation in zone 3 were obtained. To establish zone 2 conditions, Po was decreased until no further increase in flow was noted. To measure the pressure volume profile in zone 3, Pi was decreased to Po, obtaining zero flow. Inflow pressure and Po were then simultaneously increased by an equal amount, resulting in a vascular volume change that was recorded as a weight gain with flow remaining zero. Three steps up and down were recorded. Weight changes occurring in the first 35 seconds were attributed to vascular volume changes only.

Calculations and Data Analysis

From the multiple pressure flow points, one variable linear regression analysis was used to obtain the best equation representing the pressure/flow relation. The

Table 1. Lobar Weights and Eurocollins Solution Infusion Data: Protocol 1[a]

Group	No. of Dogs	Dry Weight (g)	WW/DW	Volume[b] (L)	Time (min) Infusion	Time (min) Rewarm	Temperature (°C) In	Temperature (°C) Out
A								
I	6	12.7 ± 1.7	4.6 ± 1.0					
II			5.8 ± 1.0					
B								
I	6	15.5 ± 4.2	5.3 ± 0.5[c]	1.75 ± 0.3	11.3 ± 5.3	25.9 ± 6.1	4.5 ± 1.1	7.3 ± 1.8
II			5.3 ± 1.3					
C								
I	7	14.4 ± 4.0	3.8 ± 1.4[c]	1.6 ± 0.3	15.4 ± 6.4	33.3 ± 8.2	4.1 ± 1.6	7.2 ± 1.7
II			5.7 ± 2.3					

[a] Results are expressed as mean ± standard deviation. [b] Volume of Eurocollins solution perfused. [c] Significance: $p < 0.05$ for BI versus CI.

A = time control; B = oxygen on during perfusion; C = oxygen off during perfusion; I = baseline conditions; II = conditions after perfusion with Eurocollins solution or time control; WW/DW = ratio of wet to dry weight.

slope of the pressure/flow profile is interpreted by many researchers as vascular conductance (Cv); by extrapolating the high-flow straight-line portion we calculated the vascular pressure at zero flow. This represents average vascular closing pressure (Cx). Critical closing pressure (Cz) was measured under zone 2 conditions by lowering Pi to the point at which no flow was observed and then occluding the inflow tubing. The final resultant Pi was considered Cz [12]. Each maneuver was performed three times; the resulting Cv, Cx, and Cz were averaged. We determined vascular compliance (V) from the pressure/volume profile by relating the change in vascular volume to the applied pressure. Because Pi was equal to Po, the applied pressure was the difference between Pi at the beginning and the end of a step up or down in pressure. Thus, V was measured at six points, three on the way up and 3 on the way down. Because all data were paired, each dog served as its own control and paired *t*-tests were used to assess for significance. Two-way analysis of variance was used to compare parameters between groups.

Results

Results of lobar weights and details of perfusion are summarized in Tables 1 and 2. AI, BI, CI, DI, and EI represent baseline conditions, which are similar for each group. AII, BII, and CII represent repeat measurements after time control, ECS with oxygen, and ECS without static oxygen inflation, respectively. DII and EII represent glycine buffer control and PGI$_2$ infusion, respectively, during ECS perfusion. In groups A, B, and C, there was no significant difference between volume of ECS perfused, time for perfusion or rewarming, and temperatures of the perfusate or effluent. The ratio of wet to dry weight was less for CI as compared with BI ($p \le 0.05$) but not different from AI. The ratio of wet to dry weight did not change from baseline after infusion with ECS. The ratio of wet to dry weight also did not change in group D, but it was significantly increased in group E after perfusion. The final ratio of wet to dry weight of EII was no different from that of DI or DII, however. Therefore, combined ECS

Table 2. Lobar Weights and Eurocollins Solution Infusion Data: Protocol 2[a]

Group	No. of Dogs	Dry Weight (g)	WW/DW	Time (min) a	Time (min) b	Time (min) c	Time (min) d	Temperature (°C) In	Temperature (°C) Out
D									
I	7	13.2 ± 2.9	5.8 ± 1.0	4.5 ± 1.7	22.6 ± 1.1	2.2 ± 1.0	27.0 ± 8	3.9 ± 0.5	7.4 ± 0.6
II			5.9 ± 1.0						
E									
I	7	13.9 ± 3.5	3.5 ± 0.9[b]	3.4 ± 2.0	21.9 ± 2.1	2.9 ± 1.5	29.7 ± 11.7	4.0 ± 0.6	7.6 ± 1.0
II			5.0 ± 0.5						

[a] Results are expressed as mean ± standard deviation. [b] Significance: $p < 0.01$ for EI versus EII.

a–d = time of preinfusion, intrainfusion, and postinfusion of either glycine buffer or prostacyclin and time to rewarm, respectively; D = glycine buffer control; E = prostacyclin infusion during Eurocollins solution perfusion; I = baseline conditions; II = conditions after perfusion with Eurocollins solution; WW/DW = ratio of wet to dry weight.

Table 3. Blood Gas Tensions and Hematocrit Measurements[a]

Group	PO_2 (mm Hg) Inflow	PO_2 (mm Hg) Outflow	PCO_2 (mm Hg)	pH	Hematocrit
A					
I	243 ± 110	295 ± 153	20.2 ± 1.7	7.48 ± 0.05	43.8 ± 6.5
II	290 ± 113	344 ± 147	20.6 ± 1.7	7.44 ± 0.03	45.8 ± 5.6
B					
I	269 ± 25	303 ± 37	20.3 ± 2.4	7.47 ± 0.06	49.2 ± 3.6
II	235 ± 31	279 ± 57	20.9 ± 5.9	7.40 ± 0.08	50.3 ± 4.8
C					
I	242 ± 78	280 ± 85	18.8 ± 5.5	7.51 ± 0.07	46.7 ± 4.5
II	296 ± 65	372 ± 74	20.5 ± 4.7	7.43 ± 0.04	47.0 ± 4.6
D					
I	. . .	352 ± 70	19.2 ± 3.4	7.56 ± 0.13	43.4 ± 5.0
II	. . .	297 ± 64	20.6 ± 3.6	7.48 ± 0.12	41 ± 7.5
EII	. . .	339 ± 76	17.6 ± 3.2	7.50 ± 0.10	42.7 ± 5.8

[a] Results are expressed as mean ± standard deviation.

A = time control; B = oxygen on during perfusion; C = oxygen off during perfusion; D = Eurocollins solution with glycine buffer control; E = Eurocollins solution with prostacyclin; I = baseline conditions; II = conditions after perfusion with Eurocollins solution or time control; PCO_2 = carbon dioxide tension; PO_2 = oxygen tension.

perfusion/PGI_2 infusion did not result in significant edema formation.

The blood gas tensions and hematocrit are summarized in Table 3. In groups D and E, only outflow blood gas tensions and hematocrit were measured at the end of ECS perfusion to assess the effect of the glycine buffer infusion. There was no difference between any variable measured within or between groups.

The results of the effect of ECS on the pulmonary circulation are summarized in Tables 4 and 5. Vascular conductance decreased after ECS perfusion by 3.7 ± 0.7 and 7.2 ± 2.3 mL/min/cm H_2O in groups B and C, respectively. This was associated with an increase in Cx of 1.2 ± 0.4 cm H_2O in group B and 2.1 ± 0.5 cm H_2O in group C (Fig 2). There was no significant difference between final Cv in groups B and C, but the final Cx of group C was greater than that of group B, indicating that the net effect of not providing oxygen during ECS was deleterious to blood flow.

In group D, ECS resulted in significant depression of Cv, as had been noted in group B under similar circumstances. Addition of glycine buffer alone had no effect on Cv. In group E, PGI_2 resulted in a much smaller decrease in Cv under zone 3 conditions and no significant change under zone 2 conditions. Average vascular closing pressure increased in group D as it had in group B, and decreased in group E. There was a significant decrease in V with ECS perfusion alone, with no change in V when

Table 4. Vascular Effect of Eurocollins Solution: Effect of Oxygen[a]

Group	Pa (cm H_2O)	Po (cm H_2O)	Cv (mL/min/cm H_2O)	Cx (cm H_2O)
A				
I	4.75 ± 0.4	14	22.4 ± 10.0	15.7 ± 1.7
II			21.9 ± 9.8	16.2 ± 2.7
B				
I	4.4 ± 1.0	13.9 ± 1.7	22.6 ± 3.2	13.7 ± 2.7
II			18.9 ± 4.7[b]	14.9 ± 2.7[b,c]
C				
I	5.0	14.2 ± 1.7	21.3 ± 8.1	13.6 ± 3.7
II			14.1 ± 6.4[d]	16.0 ± 2.0[c,d]

[a] Results are expressed as mean ± standard deviation. [b] Significance: $p < 0.01$ for BI versus BII. [c] Significance: $p < 0.05$ for BII versus CII. [d] Significance: $p < 0.05$ for CI versus CII.

A = time control; B = oxygen on during perfusion; C = oxygen off during perfusion; Cv = vascular conductance; Cx = average vascular closure; I = baseline conditions; II = conditions after perfusion with Eurocollins solution or time control; Pa = transpulmonary pressure; Po = outflow pressure.

Table 5. Vascular Effect of Eurocollins Solution and Prostacyclin[a]

Group	Zone 3[b]		Zone 2[b]			
	Cv (mL/min/cm H_2O)	Cx (cm H_2O)	Cv (mL/min/cm H_2O)	Cx (cm H_2O)	Cz (cm H_2O)	V (mL/cm H_2O)
D						
I	28.3 ± 9.0[c]	14.3 ± 1.1[c]	23.3 ± 11.3[c]	11.5 ± 2.0	8.1 ± 1.0	1.63 ± 0.7[c]
II	21.6 ± 8.2	15.6 ± 1.3	16.1 ± 7.4	11.5 ± 1.7	8.6 ± 1.4	1.25 ± 0.5
E						
I	30.0 ± 11.8[c]	14.3 ± 1.7[c]	27.8 ± 12.0	11.0 ± 2.0[d]	7.1 ± 1.0	1.39 ± 0.8
II	27.1 ± 10.7	13.8 ± 4.5	27.1 ± 11.3	12.1 ± 1.3	8.0 ± 1.0	1.40 ± 0.7

[a] Results are expressed as mean ± standard deviation. [b] According to West and colleagues [10]. [c] Significance: $p < 0.05$ for I versus II. [d] Significance: $p < 0.01$ for I versus II.

Cv = vascular conductance; Cx = average vascular closure; Cz = critical vascular closure; D = Eurocollins solution with glycine buffer control; E = Eurocollins solution with prostacyclin; I = baseline conditions; II = conditions after perfusion with Eurocollins solution; V = vascular compliance.

PGI_2 was infused with the ECS. Prostacyclin therefore maintained blood flow and V at baseline levels after ECS perfusion.

Comment

Previous work on the effectiveness of various aspects of lung perfusion and preservation has used mainly the ability of a reimplanted or transplanted lung to independently maintain the animal as the method of assessment [13, 14]. There is merit in this approach: once a native lung has been replaced by a transplanted lung it must be fully capable of supporting the recipient because there is no artificial organ to fall back on. This approach does not lend itself to an in-depth physiological assessment of the effect of the perfusion or preservation methods alone, however, because it is hampered by the added complications of infection and rejection. The isolated lower lobe preparation answers many of these concerns because baseline measurements are made, an intervention is introduced, and the lobe can be returned to baseline conditions. The interventions we tested in this experiment were perfusion of the lobe with ECS with and without static oxygen inflation and evaluation of the potential protective effects of PGI_2 on blood flow.

With time, slow deterioration occurs in isolated lobes, with edema accumulation resulting in part from the complete absence of lymphatics. Because this has a significant effect on all functional variables being measured, time controls were necessary. In groups A, B, and C, the level of hydration did not increase significantly, and the blood gases, hematocrits, level of hypothermia, volume of perfusate, and times required for infusion and rewarming were comparable in all groups. In groups D and E, glycine buffer did not have an appreciable effect on pH.

Under zone 3 conditions, ECS caused a significant decrease in Cv in both groups B and C; the decrease in group C was double that in group B. This difference did not reach statistical significance, however. Average vascular closing pressure increased in groups B and C and was statistically greater in group C. Therefore, the pressure cost of vascular perfusion is increased after infusion of ECS, and this was independent of the hypothermic effect because the lobes were fully rewarmed. The recovery period typically lasted about 30 minutes, but the vascular changes were still present after three hours in several lobes. Veith and colleagues [4] reported that pulmonary vascular resistance increased with transplantation. Yacoubian and co-workers [5] also reported an acute increase in pulmonary vascular resistance with reimplantation that gradually returned to normal by 6 weeks. These were both acute transplantation/reimplantation experiments and hypothermic perfusion was not used by either group of investigators, suggesting that the increase in pulmonary vascular resistance occurs as either an acute reperfusion injury or a subsequent rejection phenomenon. Our data suggest that ECS by itself, perhaps independent of hypothermia, causes an increase in vascular resistance. Perfusion with warm ECS was not attempted because lungs are known to function very poorly if hypothermia is not used.

Statically inflating the lobe with oxygen during perfusion appears to be beneficial. The mechanisms are unknown, but two possibilities may be important. The hypothermic lung may require oxygen for metabolic purposes, and keeping the lobe inflated may allow more uniform distribution of ECS. This latter possibility has some support in that the time required for perfusion was slightly longer in group C. Prostacyclin as an adjuvant to ECS perfusion had a beneficial effect on Cv under both zone 2 and 3 conditions, and this was associated with a significant decrease in Cx. Prostacyclin therefore maintained blood flow, and no increase in vascular resistance was noted.

From these data, some observations about the mechanisms and sites of action of ECS and PGI_2 can be made. The pulmonary circulation can be divided into extraalveolar and alveolar compartments. The extraalveolar compartment consists of two components, the pulmonary artery and its prearteriolar divisions and the venous system. Brower and colleagues [15] showed that the extraalveolar compartment makes minor contributions whereas the alveolar compartment is the major site of vascular compliance. A 23% reduction in compliance (V)

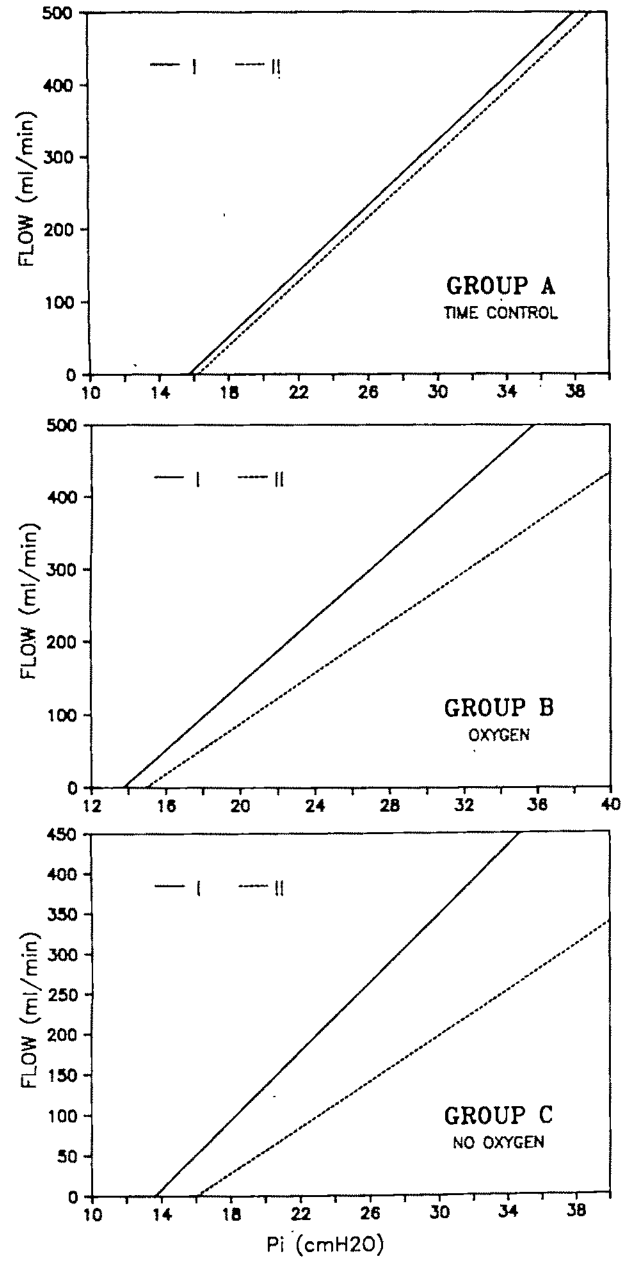

Fig 2. Flow in milliliters per minute on the ordinate is plotted against inflow pressure (Pi) in centimeters of water on the abscissa. The solid line *represents baseline conditions. Upper panel: No change occurred with time. Middle panel: Perfusion with Eurocollins solutions while oxygen is provided results in a significant increase in average vascular closure and decrease in vascular conductance. Lower panel: Perfusion with Eurocollins solution without oxygen results in a greater increase in average vascular closure and decrease in vascular conductance.*

was observed with ECS alone but was completely prevented by addition of PGI_2. Blood flow into the compliant alveolar compartment is regulated by the precapillary arteriole. The changes in Cv and Cx observed with ECS alone indicate both a shift to the right and a decrease in slope of the pressure/flow curve. Recently, published model predictions of the pulmonary circulation by Bshouty and Younes [16] showed that obstruction causes a decrease in slope while increased tone causes a parallel shift to the right in pressure flow curves. This suggests that ECS caused both vascular obstruction and increased tone. With the addition of PGI_2, there was still a slight decrease in slope, but this was associated with a shift to the left and the net result was that no change in blood flow occurred. This is supported by the zone 2 Cv observation, although Cx increased slightly. Critical closing pressure was not altered by ECS perfusion and is similar to Cz described in the literature for normal lungs [12].

The exact site of action of PGI_2 in the lungs is unknown, but it is found in abundant supply in association with vascular endothelium of larger vessels, originates from pulmonary endothelium, and although not readily degraded during passage through the lungs is ultimately catabolized by pulmonary 15-hydroxydehydrogenase [11, 17]. Prostacyclin may therefore be capable of reaching pulmonary vascular smooth muscles through "myoendothelial junctions" [17]. Therefore, ECS probably has a direct action on the extraalveolar vessels, causing increased tone and obstruction with reduction of total vascular compliance. Prostacyclin prevents this by acting directly on vascular smooth muscle. By inhibiting platelet aggregation, it could also affect the fluidity of blood and contribute to improved blood flow through this mechanism.

Cold ECS perfusion in canine lobes resulted in an increased pressure cost of vascular perfusion. This appears to result predominantly from an increase in vascular tone and obstruction in extraalveolar vessels. This supports the observation of increased pulmonary vascular resistance in in situ experiments [4, 5]. If left untreated, this could lead to acute cor pulmonale and resultant early graft failure. The findings also provide a sound theoretical basis for oxygen inflation and for combining ECS perfusion with PGI_2 infusion of donor lungs.

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First Human Use of the Hemopump, a Catheter-Mounted Ventricular Assist Device

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The Hemopump, a catheter-mounted, temporary ventricular assist device, consists of an external electromechanical drive console and a disposable, intraarterial axial-flow pump (21F). Power is transmitted percutaneously to the pump by a flexible drive shaft within the catheter. The device is positioned in the left ventricle by way of the femoral artery approach or through the ascending aorta. Blood is drawn from the left ventricle through the transvalvular inlet cannula and pumped into the aorta. As of December 1988, the Hemopump had successfully supported the circulation of 7 patients (5 men, 2 women) ranging in age from 44 to 72 years (mean age, 59 years) and suffering from cardiogenic shock (cardiac index <2.0 L/min/m^2). Indications for use included failure to be weaned from cardiopulmonary bypass in 4 patients, acute myocardial infarction in 1, severe cardiac allograft rejection in 1, and donor heart failure in 1. Duration of support ranged from 26 to 113 hours (mean, 66 hours). Although 5 patients demonstrated transient hemolysis, none experienced infection, thrombosis, or vascular injury. Hemodynamic variables improved in all patients during support by the device. As of December 1988, 5 of the 7 patients were alive more than 30 days after support had been discontinued, and 3 of these patients were discharged from the hospital. On the basis of our initial clinical results, the Hemopump, which does not require a major surgical procedure for insertion, provides effective, temporary circulatory support in patients with potentially reversible cardiac failure.

(Ann Thorac Surg 1990;49:299–304)

In 1964 DeBakey [1] was first to insert a mechanical cardiac assist pump in a procedure that required an open chest operation. The clinical application of the intraaortic balloon pump by Kantrowitz [2] in 1967 simplified the implementation of mechanical assistance, and its widespread use since then has shown that ventricular recovery can be achieved in many instances of postcardiotomy or postmyocardial infarction ventricular compromise. In 1975 Norman and associates [3, 4] introduced an abdominal left ventricular assist device that was used only in patients who suffered total loss of ventricular function after an open heart operation. Ventricular function invariably improved in patients who survived 48 hours of support; however, patients did not recover because of complications related to the major operative procedure required to implant the device. The results of left ventricular support are expected to improve with one of the most recent assist devices developed, the Hemopump (Nimbus Medical, Inc, Rancho Cordova, CA) [5], an intraarterial transvalvular axial flow pump that is undergoing initial clinical trials. This device supplements left ventricular function, providing blood flows of 3.5 to 4.0 L/min, markedly decreasing ventricular work while supplying the basic circulatory requirements of the body at rest. The pump can be implanted with a minimal operative procedure [6] and has had few complications associated with its use. In this report, we review our initial clinical experience with the Hemopump.

Material and Methods

From April 23 to December 31, 1988, 7 patients with cardiogenic shock (cardiac index <2.0 L/min/m^2) were treated with the Hemopump. These patients included 5 men and 2 women, whose ages ranged from 44 to 72 years (mean age, 59 years). Body surface area ranged from 1.68 to 2.13 m^2 (mean, 1.86 m^2). All patients were entered in the study according to the following specific guidelines:

Inclusion Criteria
- Pulmonary capillary wedge pressure >18 mm Hg
- Systolic aortic pressure <90 mm Hg or mean aortic pressure <60 mm Hg
- Cardiac index <2 L/min/m^2
- Failure of maximal drug and volume therapy

Exclusion Criteria
- Aortic valvular or aneurysmal disease
- Significant blood dyscrasia
- Approved cardiac transplant candidate
- Prosthetic aortic valve
- Aortoiliac occlusive disease

Informed consent was obtained in accordance with the guidelines of the Food and Drug Administration and the Institutional Review Board of the Texas Heart Institute/St. Luke's Episcopal Hospital. The specific indication for the use of the Hemopump in each patient is listed in Table 1,

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Table 1. Hemopump Patient Profiles

Patient Demographics					
Patient No.	Age (yr)	Sex	BSA (m^2)	Indications	Operative Procedures[a]
1	62	M	1.89	Severe cardiac allograft rejection	None
2	61	M	1.68	AMI	None
3	72	F	1.78	Failure to wean from CPB	Emergency reoperation, CAB × 3
4	50	M	1.92	Acute allograft failure, failure to wean from CPB	Orthotopic cardiac transplantation
5	44	F	1.76	Failure to wean from CPB	Emergency reoperation, CAB × 3 + LVA
6	66	M	1.88	Failure to wean from CPB	CAB × 3 + LVA + mitral valvoplasty
7	58	M	2.13	AMI, failure to wean from CPB	Emergency reoperation, CAB × 2

[a] Operations requiring CPB immediately before Hemopump implantation. [b] Less than 24 h before implantation. [c] IABP support not attempted. [d] Died of lymphoma after transplantation.

AMI = acute myocardial infarction; BSA = body surface area; CAB = coronary artery bypass; CPB = cardiopulmonary bypass; IABP = intraaortic balloon pump; LVA = left ventricular aneurysmectomy.

as is the status of the patient before pump implantation. The hemodynamic data for each patient at the time of implantation were as follows: patient 1 had a cardiac index of 1.85 L/min/m^2, and in patient 2 it was 1.96 L/min/m^2. Patients 3 through 7 could not be weaned from cardiopulmonary bypass and had no measurable cardiac output. Vasoactive drug therapy included intravenous infusions of epinephrine (7 patients), calcium chloride (6), dopamine (3), dobutamine (3), sodium bicarbonate (4), and other agents (4). All patients received some combination of at least three and as many as five of these agents.

Description of the Hemopump

The Hemopump consists of three basic elements: a pump assembly, a high-speed motor, and a control console. The disposable pump assembly (Fig 1) integrates all blood-contacting surfaces into a single system. The inlet cannula, which is made of flexible silicone rubber, measures 20 cm in length and 7 mm in diameter. It is reinforced with a helical spring to prevent kinking and has a beveled, radiopaque tip to facilitate placement across the aortic valve (Fig 2). The inlet cannula is connected directly to the blood pump housing, which has an outer diameter of 7 mm (21F) and is made of highly polished, thromboresistant stainless steel, as is the pump impeller. Power to the axial flow pump, located within the housing, is transmitted by a flexible drive shaft enclosed in a 9F polymeric sheath. The external end of the drive shaft is connected to an external reusable high-speed motor. When the device is activated, the pump impeller, which spins at 15,000 (pump speed 1) to 27,000 (pump speed 7) rpm, provides unidirectional, nonpulsatile flow. Blood is thus drawn from the left ventricle and propelled by the pump into the aorta. Maximum flow through the pump approaches 4 L/min and is primarily related to two variables: (1) external resistance to flow, ie, afterload or systemic vascular resistance, and (2) the inlet cannula position within the left ventricular cavity.

Also enclosed in the drive shaft sheath is a purge fluid system that uses 40% dextrose in water. This fluid lubricates the drive shaft and the hydrodynamic bearings, which support the rotating elements of the blood pump. Because of the high pressure of the purge fluid, generated by a roller pump on the console, flow across the drive shaft seal is outward. Thus, the purge fluid flow prevents the entry of blood into the drive mechanism. Because the purge fluid flow rate is low (approximately 200 mL/day) and because only a portion of the purge fluid flows across the seal into the systemic circulation, its effect on the intravascular volume is considered negligible.

The control console (Fig 3) powers and regulates the blood pump and the roller pump in the purge fluid system. Fail-safe mechanisms necessary for clinical use are also provided. These include warning signals for external alternating current power loss (an internal battery provides 30 minutes portable operation) and abnormal changes in motor current and purge pressure. To facilitate pump weaning, the console provides seven graded pump speeds, as well as visual display of calculated pump flow. This flow is calculated as a function of pump speed and mean aortic pressure. For example, at a pump speed of 7 (27,000 rpm) and a mean aortic pressure of 50 mm Hg, calculated pump flow is 4 L/min. The console, which weighs approximately 11.4 kg, can be easily carried or mounted on a rolling stand.

Methods of Implantation

The Hemopump was implanted through the femoral artery in 4 patients and through the ascending aorta in 3. The techniques have been described in detail [6]. After the pump has been inserted and the patient has been transferred to the intensive care unit, the position of the device is once again confirmed radiographically (Fig 4).

Anticoagulative Therapy

Heparin was administered intravenously to maintain an activated clotting time of 1.5 to 2 times control. If the patient had postoperative blood loss or coagulopathy, anticoagulative therapy was withheld until hemostasis was achieved.

Table 1. Continued

	Status Before Implantation				Status After Implantation	
Duration of Shock (h)	Failed IABP	Acute Renal Failure	Cardiac Arrest[b]	Weaned From Hemopump	Survived (≥30 days)	Discharged
24	No[c]	Yes	No	Yes	Yes	Yes
24	Yes	Yes	Yes	No	No	No
12	No[c]	No	No	Yes	Yes	Yes
2	No[c]	Yes	Yes	Yes	Yes	No[d]
2	Yes	Yes	No	Yes	No	No
1	Yes	No	No	Yes	Yes	Yes
1	Yes	No	No	Yes	Yes	No

Hemodynamic Monitoring and Management

All patients were monitored with continuous electrocardiographic tracings, radial arterial lines, and pulmonary artery catheters. Cardiac output determinations were made using standard thermodilution techniques. All attempts were made to provide optimal pump flow, including maintaining adequate intravascular volume and left ventricular filling pressures and reducing systemic vascular resistance to the range of 600 to 800 dynes · s · cm^{-5}, primarily through a continuous intravenous sodium nitroprusside infusion. Additionally, the use of inotropic agents was minimized.

Hematologic Studies

All patients were carefully monitored for rheologic abnormalities using serial determinations of plasma free hemoglobin and serum haptoglobin levels, fibrin split products, fibrinogen levels, and platelet and hemoglobin levels. Peripheral blood smears were also routinely examined for evidence of hemolysis.

Device Weaning and Removal

Once the patient's heart has adequately recovered, ie, when the cardiac index is greater than 2.2 L/min/m^2 with minimal inotropic support, pump speed is gradually reduced from speed 7 to speed 1. The pump is not stopped until immediately before removal. Heparin is not reversed. The device is removed by way of the graft, after which the cannulation site is inspected for evidence of endothelial damage or thrombus formation. The arteriotomy/aortotomy is then repaired using a continuous polypropylene suture, and the remaining incision is closed in standard fashion.

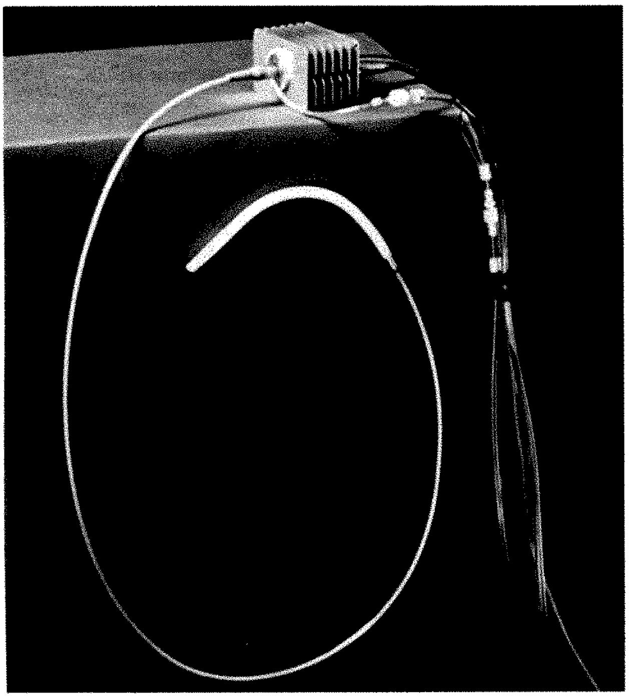

Fig 1. Disposable pump assembly consists of an inlet cannula, axial flow blood pump, flexible drive shaft enclosed in a polymeric sheath, and motor rotor.

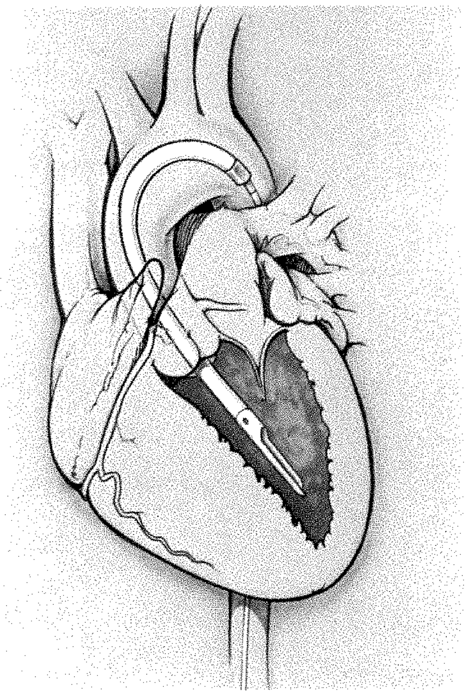

Fig 2. The beveled, radiopaque tip of the inlet cannula facilitates placement across the aortic valve.

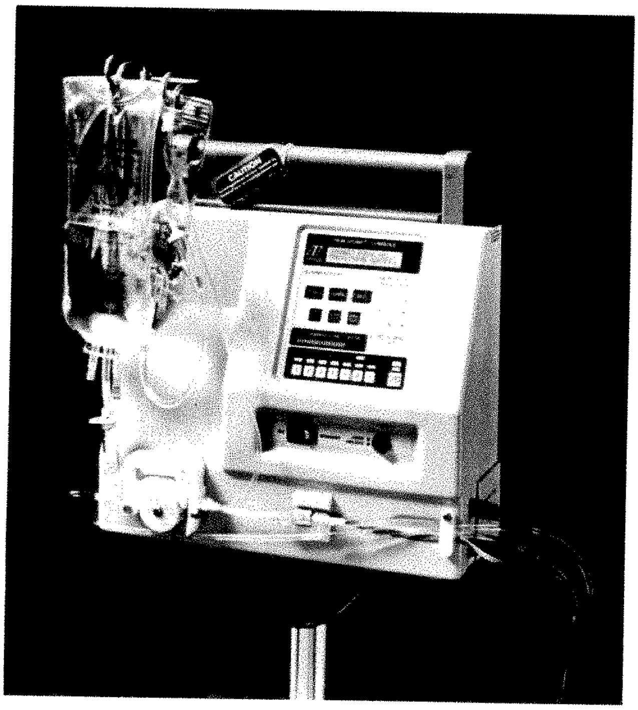

Fig 3. The control console, which provides power for the blood pump, also contains roller pumps for purge fluid delivery.

Results

The duration of Hemopump support ranged from 26 to 113 hours (mean, 66 hours). The operative time required for device implantation, including confirming the position of the pump by fluoroscopy, was approximately 15 minutes. All of the patients tolerated the implantation procedure well, and none experienced major surgical complications.

The hemodynamic status of each patient improved immediately on initiation of Hemopump support. The mean hemodynamic variables for all patients during the first 12 hours and during the last 12 hours of Hemopump support are shown in Table 2. The change in the vasoactive drug therapy of each patient during the course of Hemopump support included a decrease in inotropic drug therapy and an increase in afterload reduction therapy in 5 patients (Table 3). In 1 patient, vasoactive drug therapy remained fairly constant throughout the duration of Hemopump support. Increased inotropic support was required in only 1 patient (patient 3), although he also had increased afterload reduction therapy. Five of the 7 patients were alive more than 30 days after device insertion. Three of these patients have been discharged from the hospital and have returned to their normal activities. Neither of the 2 patients who died within 30 days of insertion were being supported by the device at the time of death. One patient was found to have irreversible biventricular failure and died four hours after the device was electively removed. A second patient, who had remained hemodynamically stable for two days after device removal, died unexpectedly of sudden cardiac arrhythmia.

Table 2. Hemodynamic Variables During Hemopump Support

Variable	Initial 12 h[a]	Final 12 h[a]
Cardiac index (L/min/m^2)	1.73 ± 0.59	2.77 ± 0.36
Mean aortic pressure (mm Hg)	59 ± 13	69 ± 10
Mean pulmonary capillary wedge pressure (mm Hg)	17 ± 5	14 ± 4
Urine output (mL/h)	18 ± 21	74 ± 48

[a] Values represent mean ± standard deviation.

Complications directly related to the use of this device were minimal. In 2 patients, the pump inlet cannula was ejected by the heart from the left ventricle; however, the cannula was easily repositioned at the bedside in both instances with no observed adverse effect. The drive shaft fractured in four cases, and pump support was terminated. In all cases, the fracture was contained within the central core of the drive shaft sheath. After removal of the device, all 4 patients remained hemodynamically stable. No clinical evidence of valvular damage or vascular injury was present, and no patients experienced thromboembolic episodes or infection. Device-related bleeding episodes resulting from anticoagulative therapy were dif-

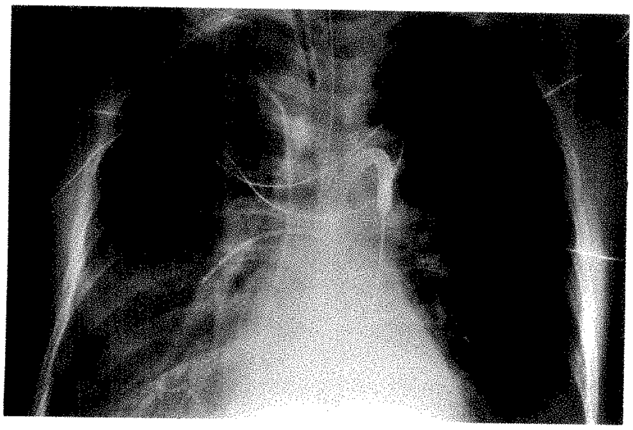

Fig 4. Roentgenogram of Hemopump placed by way of the femoral approach, revealing placement of the inlet cannula within the left ventricle and the pump in the descending thoracic aorta. When the aortic approach is used, the pump resides in the ascending aorta.

Table 3. Changes in Inotropic and Afterload Reduction Therapy During Hemopump Support

Patient No.	Inotropic Therapy	Afterload Reduction Therapy
1	Decrease	Increase
2	Decrease	Increase
3	Increase	Increase
4	No change	No change
5	Decrease	Increase
6	Decrease	Increase
7	Decrease	Increase

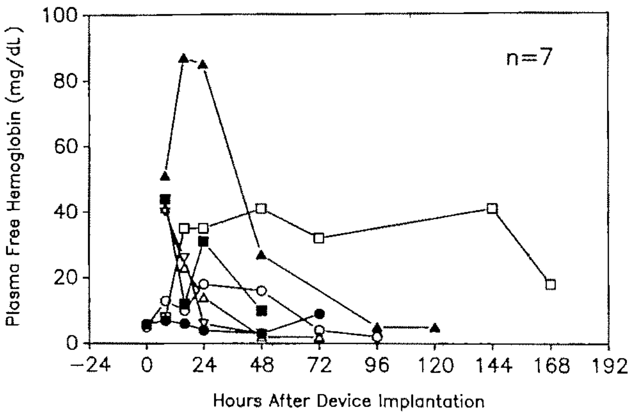

Fig 5. Plasma free hemoglobin levels in the 7 patients supported with the Hemopump.

ficult to distinguish from bleeding resulting from other causes, eg, prolonged cardiopulmonary bypass times in some surgical patients. In none of the patients did bleeding at the insertion site develop.

Hemolysis, as indicated by serial determinations of plasma free hemoglobin levels, was present in mild to moderate degrees in 5 patients during Hemopump support (Fig 5). Plasma free hemoglobin levels remained within normal limits (<10 mg/dL) throughout the course of Hemopump support in 2 patients. In all but 1 patient, plasma free hemoglobin levels returned to normal within 24 hours after device removal.

Comment

Our initial clinical experience with the Hemopump, a new left ventricular support system, has been encouraging. This system can be rapidly and safely implemented, and the circulatory support provided can be effective in allowing the ventricle to rest and potentially to recover.

Over the last decade, the ability to reverse some of the effects of acute heart failure using various cardiac assist devices has been shown [7, 8]. Because the implantation of many of these devices has required a major operative procedure in patients whose conditions are already severely compromised, survival has been adversely affected. For example, the common surgical problems of bleeding and infection are exacerbated by the need for prolonged cardiopulmonary bypass during device implantation.

Although less invasive support systems have been used, no device that can be implanted through the intraarterial approach has been as effective in supporting the circulation as the Hemopump [9, 10]. The intraaortic balloon pump only augments left ventricular function, whereas the Hemopump is capable of temporarily supplying circulatory requirements even in the total absence of effective left ventricular ejection (Table 1). In 4 of the 7 patients, intraaortic balloon pump support had been attempted and had failed. The hemodynamic status of all 7 patients improved quantitatively, and none died while being supported by the device. We believe that the patients' improvement was due specifically to the support provided by the Hemopump and subsequent ventricular recovery. All the patients had been in critical condition at the time of device implantation and had multiple risk factors for early operative mortality [11–13]. These risk factors included advanced age, emergency operation, complex operation, reoperation, multiple-vessel disease, acute renal failure, prolonged shock, and even prior cardiac arrest. Thus, the probability that any of these patients would have survived without some form of escalated mechanical circulatory support was minimal.

Optimal management of patients on the Hemopump is closely related to pump performance. Because the pump output varies inversely with mean aortic pressure, we have routinely employed intravenous infusion of sodium nitroprusside to maintain the mean aortic pressure at 50 to 60 mm Hg. At these pressures, pump flow typically ranges from 3.5 to 4.0 L/min. Concomitantly, such therapy minimizes native cardiac afterload and may thus effect cardiac recovery. Moreover, because the flow provided by the Hemopump appears adequate for the basic circulatory needs of most patients even without assistance from the heart, the requirement for catecholamine therapy is usually reduced. In this way, the adverse effects of prolonged, intense catecholamine therapy are avoided, and left ventricular recovery may be enhanced.

Device-related complications have been minimal. Evidence of hemolysis, which was a particular concern because of high pump speeds (maximum, 27,000 rpm), was minimal and occurred in 5 of the 7 patients. However, it should be noted that all of these patients had also undergone prolonged support with cardiopulmonary bypass, a well-documented cause of hemolysis. Thus, the extent to which hemolysis was due to the Hemopump remains uncertain. We are encouraged by the fact that in 2 patients in whom cardiopulmonary bypass was not used, plasma free hemoglobin levels remained within normal limits. This finding supports the results of our extensive preclinical animal studies, in which hemolysis specifically related to the Hemopump was inconsequential [5]. Bleeding specifically related to the Hemopump was not seen; the 2 patients in whom Hemopump implantation was the sole procedure performed did not experience bleeding. To correct the problem of drive shaft fracture, the inlet cannula has been lengthened from 20 to 26.7 cm. This modification allows the pump to be positioned in the descending thoracic aorta rather than in the aortic arch and eliminates severe bending of the drive shaft. No further drive shaft fractures have occurred. In confirmation of preclinical studies [5, 9, 10], transvalvular placement of the device did not cause aortic insufficiency or reduce coronary flow in this series of patients. Furthermore, injury to the aorta and the aortic valve, thromboembolic episodes, and infection were not evident.

A potential complication of this device, which we have not encountered, is the development of pump dependence beyond the current protocol limiting support to 14 days. If this were to occur, we would replace the initial Hemopump with either another Hemopump or another left ventricular support device [14, 15]. Right heart support is not currently available.

Based on our early clinical experience, the Hemopump, with its small size, short insertion time, and minimal associated morbidity, is a useful tool in the treatment of patients with potentially reversible cardiac failure.

In the future, broader application of this device will be explored in settings such as cardiac catheterization laboratories or emergency rooms. Smaller versions of the Hemopump, designed for percutaneous insertion, are being developed and should further extend its application.

Addendum

Of the 5 patients who lived more than 30 days after Hemopump support, 1 died of lymphoma and 1 died of arrhythmia (2 months and 6 months, respectively, after device removal). The 3 patients who were discharged from the hospital were alive and well at follow-up in October 1989.

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Cardiac Hemangioma With Papillary Endothelial Hyperplasia: Report of a Resected Case and Review of the Literature

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A case of left atrial hemangioma with papillary endothelial hyperplasia in a 42-year-old man is reported. With the aid of cardiopulmonary bypass, the tumor was resected, and the patient is well 22 months after operation. The clinical symptoms at initial examination, operative procedure, and pathological findings are reported, and the diagnostic and therapeutic approaches to cardiac tumors are described briefly. A review of surgically treated hemangiomas is also given.

(Ann Thorac Surg 1990;49:305–8)

Among the rarest findings in cardiology and cardiac surgery are primary cardiac tumors. According to Straus and Merliss [1], their incidence at autopsy ranges from 0.001% to 0.03%. About 75% are benign and 25% are malignant. Among the benign tumors, myxomas are the most common type, constituting more than 50% of cases. Other benign cardiac tumors are rare and include fibroma, lipoma, rhabdomyoma, hemangioma, papillary fibroelastoma, theratoma, mesothelioma of the atrioventricular node, granular cell tumor, neurofibroma, and lymphangioma. Sarcomas are the most frequent malignant heart neoplasms; of these, angiosarcoma and rhabdomyosarcoma are the most common types [2]. We report a case of a hemangioma with papillary endothelial hyperplasia arising in the left atrium that was successfully removed with the aid of cardiopulmonary bypass.

A 42-year-old man was admitted to the hospital because of a 1-month history of progressive abdominal distention, exertional dyspnea, and pleuritic chest pain in the right infraclavicular area. The patient had a long history of heavy smoking and alcohol intake but no other notable clinical history.

On admission in June 1987, the patient's temperature was 36.2°C and his blood pressure was 110/80 mm Hg; all pulses were present at a regular rate of 88 beats per minute. On auscultation, cardiac sounds were distant with no murmurs, and breath sounds were normal. The abdomen was distended, and a positive hepatojugular reflex was noted. A chest roentgenogram showed cardiomegaly and signs of pulmonary venous congestion. An electrocardiogram showed normal sinus rhythm with low voltage and nonspecific T-wave changes.

Results of laboratory tests included a hematocrit of 46.4% and a white blood cell count of 12,400/mL with 83% neutrophils, 17% lymphocytes, and 3% monocytes. The serum lactic dehydrogenase, alkaline phosphatase, and transaminase levels were normal. The total serum bilirubin level, serum protein levels, and coagulation test were also normal. Other blood tests and urine analysis were within normal limits. Ultrasound examination of the abdomen showed intraperitoneal free fluid, mild enlargement of the liver and spleen, normal kidneys, and a 2 × 2-cm mass in the left hepatic lobe, consistent with an angioma. A paracentesis was performed, and 2,000 mL of a transudate-type fluid was aspirated. Because of the patient's enlarged heart and clinical symptoms, a two-dimensional echocardiogram was performed, disclosing a large mass filling the left atrium that invaded or compressed the right atrium (Fig 1).

At operation, the heart was approached by median sternotomy. The left atrium was markedly enlarged. Digital examination through a pursestring suture in the right atrial appendage disclosed a bulging interatrial septum. Total cardiopulmonary bypass with moderate hypothermia was instituted. The left atrium was opened behind the interatrial groove, and the left atrial cavity was found to be almost entirely filled by a tumor attached to the atrial wall. We resected the tumor, preserving the mitral valve and taking special care to avoid perforation of the free atrial walls. We then performed a right atrial incision and opened the atrial septum to remove the tumor completely. We closed the septum with double 3-0 polypropylene running suture.

The patient's postoperative recovery was uneventful, and he was discharged 15 days after the operation. Twenty-two months later, when the patient was symptom-free, working full-time, and without medication, a two-dimensional echocardiogram showed no evidence of cardiac tumor (Fig 2).

The resected specimen consisted of a 40-g reddish spongy mass (8 × 6 × 5 cm). Microscopic examination showed it to be composed of wide cavernous vascular spaces dissecting the auricular muscular wall to a limited extent. Large areas showed organized thrombi and papillary structures composed of a central core of connective tissue covered by endothelial cells. In these areas, and in

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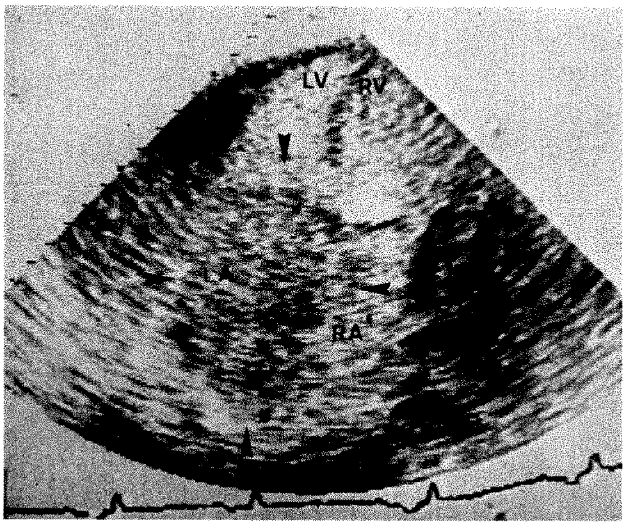

Fig 1. Preoperative two-dimensional echocardiogram showed a mass (arrows) occupying the left atrium (LA). (LV = left ventricle; RA = right atrium; RV = right ventricle.)

the cavernous cavities, the endothelial lining was composed of flattened cells with attenuated cytoplasm and small regular normochromatic nuclei. No cellular atypia or mitotic figures were noted. The final diagnosis was left atrial hemangioma with endothelial hyperplasia (Figs 3, 4).

Comments

Hemangiomas of the heart are rare. They are composed of a benign proliferation of endothelial cells that histologically are identical to hemangiomas elsewhere in the body [2]. Our case represents a cavernous hemangioma containing papillary areas resembling those described by Masson [3] as vegetant intravascular hemangioendothelioma and also known as Masson's pseudoangiosarcoma [4] or intravascular papillary endothelial hyperplasia [5]. This lesion is characterized by a florid proliferation of benign endothelial cells forming papillary structures confined within vascular spaces, which can mimic an angiosarcomatous proliferation [4]. It can occur either as a pure lesion or as a secondary change in a preexisting vascular process such as cavernous hemangioma or pyogenic granuloma [3]. This special type of lesion has been described in several anatomical regions, particularly the skin and soft tissues [3–6]. Our case represents a secondary form of this lesion in which the papillary components predominated in the cavernous areas.

Hemangiomas may occur at any age; clinical symptoms depend on tumor location [2]. With the widespread routine use of echocardiography, the ability to diagnose cardiac tumors is progressively improving. Noninvasive

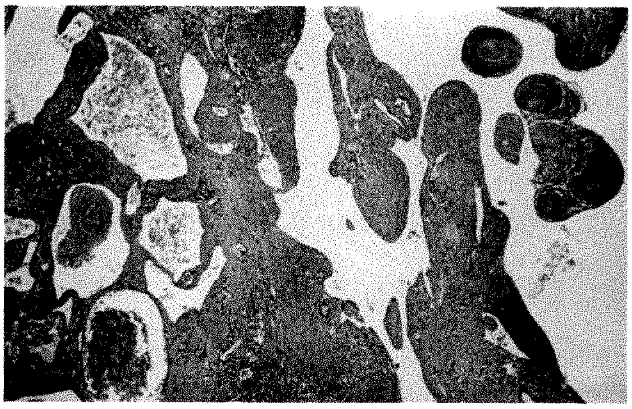

Fig 3. Microscopic section of the tumor shows areas of cavernous hemangioma on the left side and areas of papillary proliferation on the right. (Hematoxylin and eosin, ×40 before 41% reduction.)

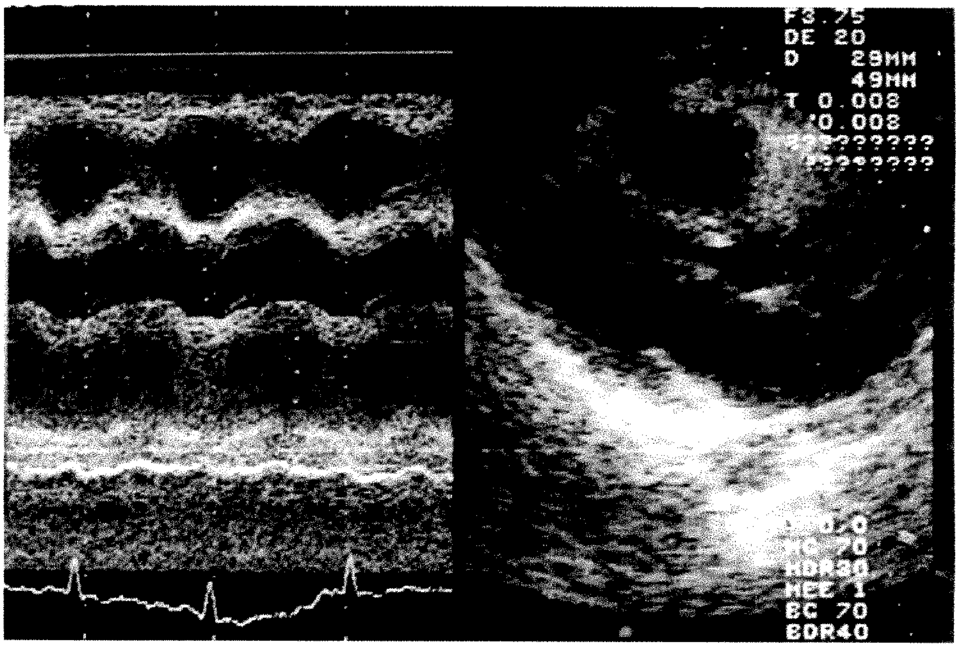

Fig 2. Postoperative echocardiogram. The M-mode (left) and two-dimensional echocardiograms (right) (parasternal view) showed no evidence of tumor.

Table 1. Patients Operated on for Cardiac Hemangioma

Author	Year	Age (yr)	Sex	Location	Operation	Pathology
Hochberg and Robinson [10]	1950	8	F	RV	Total excision	Cavernous hemangioma
Nicks [11]	1964	20	F	RV	Total excision	Vascular hamartoma
May et al [12]	1965	10	M	RA	Total excision	Vascular hamartoma
Franciosi et al [13]	1970	8	F	Apex	Biopsy	Cavernous hemangioma
Varembourg et al [14]	1971	44	F	RV	Total excision	Cavernous and capillary hemangioma
Delaye et al [15]	1972	23	M	RV	Total excision	Capillary hemangioma
Contamin et al [16]	1973	20	F	RA, RV, LV	Biopsy	Capillary hemangioma
Tabry et al [9]	1975	57	F	LA	Biopsy	Cavernous hemangioma
Stoupel et al [17]	1979	18	F	RA	Total excision	Benign hemangioma
Ilbawi et al [18]	1982	6 wk	F	RA	Total excision	Benign hemangioma
Scully et al [19]	1983	15	F	RV, VS	Biopsy	Capillary hemangioma
Geng-Sheng [20]	1984	23	F	RA	Total excision	Cavernous hemangioma
Novitzky et al [21]	1984	7	F	LV	Biopsy	Cavernous and capillary hemangioma
Novitzky et al [21]	1984	59	F	RV, PA	Total excision	Cavernous hemangioma
Albers et al [22]	1987	30	M	LV	Partial excision	Cavernous angiectasia
Weir et at [23]	1987	66	F	LA, AS	Total excision	Benign hemangioma
Fragnito et al [24]	1988	46	M	RA	Total excision	Arteriolar hemangioma
Soberman et al [25]	1988	3.5	M	VS	Total excision	Capillary hemangioma
Tadros et al [26]	1988	40	M	VS	Total excision	Benign hemangioma
Abad et al [Present study]	1989	42	M	LA, AS	Total excision	Cavernous hemangioma

AS = atrial septum; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; VS = ventricular septum.

diagnostic examination by two-dimensional echocardiogram, echo-Doppler, and computed tomography is effective and safe, eliminating the hazards and risks of embolization and systemic dissemination that may occur after heart catheterization [7].

McAllister and Fenoglio [2], in a review of 533 primary tumors and cysts of the heart and pericardium, found only 15 hemangiomas (2.8%). In a recent publication, Dein and co-workers [8] reported their 25-year experience with 42 surgically treated primary cardiac neoplasms, none of which were hemangiomas.

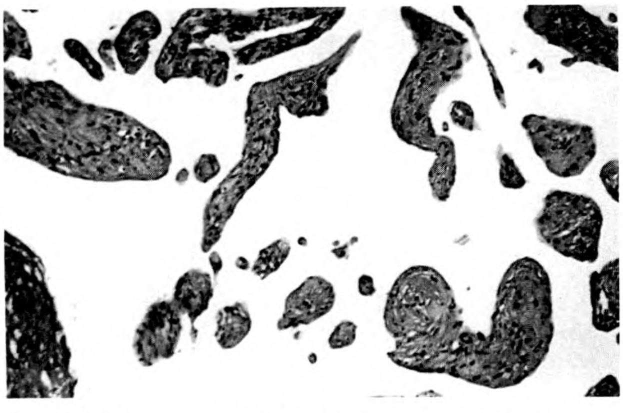

Fig 4. Papillary structures with a central core of connective tissue covered by flattened endothelial cells without nuclear atypia. (Hematoxylin and eosin, ×100 before 41% reduction.)

In 1975, Tabry and associates [9] published a case report and reviewed the world literature reporting 8 operated cases including their own [10–16]. Since then, we have found 12 more cases [17–26], including our patient (Table 1). In agreement with most investigators, we believe that complete surgical resection is the best way to treat cardiac tumors. This method provides (1) histological classification, (2) maximal tumor mass excision, and (3) improvement of clinical condition. In select cases, cardiac transplantation has been performed.

Benign resectable cardiac tumors usually have a good prognosis; however, after surgical excision, a relapsing tumor can be found. In contrast, nonresectable benign tumors and malignant growths have a poor prognosis as a consequence of ventricular arrythmias, sudden death, local progression, or systemic dissemination of the neoplastic process. Although our patient is doing well at present, the prognosis must remain guarded and periodic echocardiographic examinations will be performed to rule out recurrences.

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Dumbbell Metastatic Cystosarcoma Phyllodes of the Heart and Lung

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Cystosarcoma phyllodes is an uncommon breast tumor that rarely metastasizes. A case of dumbbell cystosarcoma phyllodes metastatic to the heart and lung diagnosed antemortem is described. The roles of diagnostic echocardiography and surgical excision are discussed. Atrial extension of a lung malignancy through a pulmonary vein is not an absolute contraindication to operation, but careful patient selection and operative planning are required.

(Ann Thorac Surg 1990;49:309–11)

Cystosarcoma phyllodes is a rare fibroepithelial neoplasm accounting for less than 1% of all breast tumors [1]. Unlike in fibroadenoma, stromal cellularity is increased. Microscopically these tumors may appear benign or malignant, and both have the ability to metastasize [2–4]. Five cases of cystosarcoma phyllodes metastatic to the heart have been reported, all diagnosed at autopsy [1]. This is a report of antemortem diagnosis of cystosarcoma phyllodes metastatic to the heart and lung. Diagnosis was by echocardiography, and treatment was by surgical resection.

A 46-year-old nulliparous Oriental woman was treated with a simple mastectomy for cystosarcoma phyllodes. Microscopically the tumor was composed of benign epithelial and high-grade undifferentiated sarcomal stromal elements. The patient was well for 2½ years and then had a flulike illness. Examination showed a holosystolic murmur (long-standing) and an early diastolic gallop sound subsequently thought to be a tumor plop. Marked clubbing was present. A chest roentgenogram showed a large bilobular mass in the right upper lobe and left atrial enlargement (Fig 1). An echocardiogram showed a multilobular, 3 × 6-cm left atrial mass that moved across the mitral valve into the left ventricle during diastole (Fig 2). There was minimal mitral regurgitation. The patient was treated with Adriamycin chemotherapy for the next 4 months. Although the pulmonary mass decreased in size, the left atrial tumor enlarged during therapy. The patient then required rehospitalization for treatment of recurrent supraventricular tachyarrhythmias and congestive heart failure. A diagnosis of Adriamycin cardiotoxicity [5] and left ventricular inflow obstruction was made. Treatment with methotrexate and 5-fluorouracil was instituted. Symptoms of shortness of breath with orthopnea and paroxysmal nocturnal dyspnea progressed, and the patient was classified in New York Heart Association class IV, living a bed-to-chair existence. Because she had increasing congestive heart failure, tachyarrhythmias, and mitral valve obstruction, an operation was performed.

In February 1986, through a median sternotomy and using cardiopulmonary bypass, the left atrium was opened, revealing a huge, multilobular cystic tumor (Fig 3) that obstructed the right superior pulmonary vein and was attached to the subvalvular supporting structures of the posterior mitral leaflet inferiorly. The posterior mitral leaflet was excised, and the tumor was cored out of the superior pulmonary vein, retracted, and cut off. We were then able to see the upper and middle lobe branch origins free of gross tumor. Frozen section of the only point of attachment to the vein wall showed no tumor invasion.

The mitral valve was replaced with a 27-mm Carpentier-Edwards supraannular prosthesis. The patient was easily weaned from cardiopulmonary bypass and had an unre-

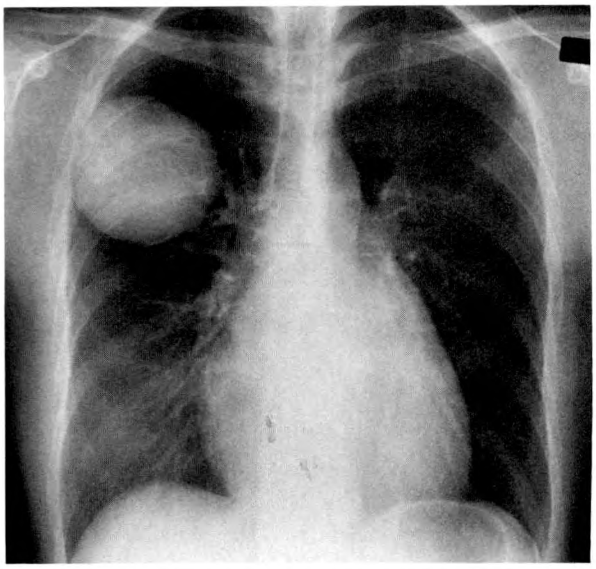

Fig 1. Chest roentgenogram showing right upper lobe tumor and left atrial enlargement.

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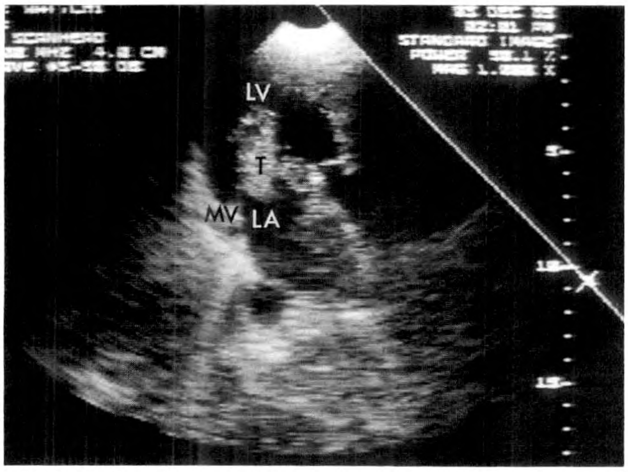

Fig 2. Two-dimensional echocardiographic examination in apical long axis view demonstrating the tumor (T) moving through the orifice of the mitral valve (MV) from the left atrium (LA) into the left ventricle (LV) with diastolic flow.

markable recovery. Ten days later, a right upper lobectomy was performed to remove the pulmonary mass, which extended into the origin of the right superior pulmonary vein. Frozen sections from the vein margin were clear of tumor.

The left atrial tumor specimen measured 10 × 5 × 2.5 cm. Microscopic examination showed an undifferentiated sarcoma with no epithelial elements, consistent with a metastatic cystosarcoma phyllodes. The attached mitral valve apparatus showed myxoid degeneration.

The right upper lobe specimen contained a tumor mass 8 cm in diameter (Fig 4) with invasion of the distal right superior pulmonary vein. Microscopic examination showed it to be identical to the heart lesion: bronchial and atrial margins, the distal centimeter of venous resection margins, and numerous lymph nodes were free of tumor.

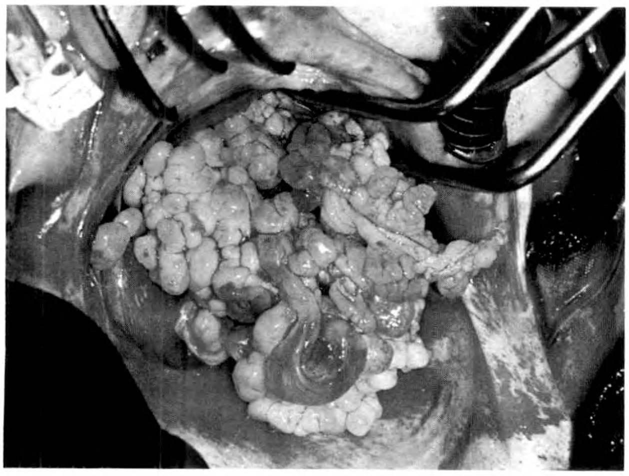

Fig 3. Cystosarcoma phyllodes erupting from the transverse left atriotomy. The right atrium is located anteriorly; the pulmonary veins, posteriorly; the cross-clamped aorta with cardioplegia infusion cannula, to the left; and the inferior vena caval cannula and cooling pad, against the diaphragm to the right.

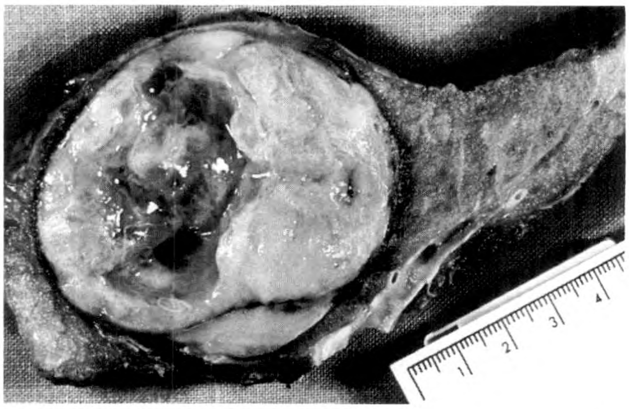

Fig 4. Right upper lobe specimen shows the well-circumscribed, yellowish-white, partially hemorrhagic and partially mucinous spongy tumor mass with central necrosis.

The patient's symptoms improved postoperatively, with a gradual increase in exercise tolerance. Four months after operation she was hospitalized for recurrent supraventricular arrhythmias, cardiac failure, low cardiac output, and respiratory distress. A complete metastatic workup had negative results. An echocardiogram showed a recurrent mass in the left atrium. A reoperation was performed with relative ease because of the previous placement of a bovine pericardial patch. There was no gross or microscopic evidence of recurrent tumor, and the prosthetic mitral valve was functioning normally. An extensive clot involving the posterior wall of the left atrium, extending into the pulmonary vein and causing partial obstruction, was removed. Administration of Coumadin was started postoperatively.

The patient again improved after operation but continued to have a degree of cardiac failure believed to be secondary to Adriamycin cardiomyopathy. Four months later and 10 months after her initial open heart procedure, she was readmitted. A large abdominal mass was confirmed by ultrasound and needle aspiration biopsy to be a metastatic cystosarcoma phyllodes arising from the pelvis. No further therapy was advised, and the patient died 3 weeks later. The family refused an autopsy.

Comment

Cystosarcoma phyllodes is an uncommon breast tumor with an unpredictable clinical course. Metastases occur in 3% to 12% of patients [1]. No reliable gross and histological features clearly separate benign from malignant tumors [2–4], but 20% to 31% are estimated to be malignant [2]. Clinical behavior does not correlate with histological appearance [2–4].

Cystosarcoma phyllodes most commonly metastasizes to lung, bone, heart, or liver (in descending order), but can involve any organ [1]. It spreads through a hematogenous route and rarely through lymphatics. There are 5 documented cases of metastatic disease involving the heart. In 1 case, the heart was the sole site of metastasis. In the other 4, the heart was one of the organs involved by widespread disease [1]. The diagnosis was established postmortem in all cases.

Metastatic tumors of the heart usually do not produce primary symptoms and are commonly diagnosed at autopsy [6]. The finding of left atrial enlargement on chest roentgenogram in our patient with a right upper lobe mass raised the possibility of left atrial involvement by tumor. Echocardiography accurately demonstrated the atrial extension preoperatively and documented its progressive increase in size during chemotherapy, even though the lung lesion was apparently responding.

No established adjuvant therapy exists for metastatic cystosarcoma phyllodes. Little benefit has been derived from irradiation, chemotherapy, and hormones [1, 3]. Surgical resection for metastatic disease to the lung can be performed if the patient is a good operative risk, the primary tumor is controlled, the lungs contain the only evidence of metastatic disease, and no other treatment modality offers the potential for reasonable palliation. Furthermore, successful resections have been reported after atrial extension of bronchogenic carcinoma [7, 8]. The choice in our patient was difficult. Although the chance for cure was small, the alternative was almost immediate death. She had a complete resection of her cardiopulmonary metastasis, but tumor biology precluded long-term survival.

The unpredictable metastatic behavior of cystosarcoma phyllodes is exemplified by the review of the Mayo Clinic experience with 10 cases by Lindquist and colleagues [3]. Two of 5 patients who died of systemic metastases had benign histology, whereas 2 of 5 patients in whom local recurrence without evidence of systemic metastases developed had malignant histology. There was 100% mortality in patients with metastatic disease [3]. However, Hart and co-workers [2] reported a woman who survived for 16 years after resection of a solitary pulmonary metastasis.

The echocardiogram was very helpful in planning our surgical approach. In dumbbell metastasis from lung to the left atrium, the intracardiac portion should be resected first to prevent the possibility of tumor embolism. Cardiopulmonary bypass may be necessary. Certainly excision of a pulmonary sarcoma without recognition of intracardiac extension can be disastrous [9]. Echocardiography may also prove a useful tool in the staging of patients with bronchogenic carcinoma when there is a possibility of extension through the pulmonary vein. Although there is an appreciable false-positive rate, especially for pericardial abnormalities, a normal echocardiogram has a predictive value of 98% and therefore assures that there will be no cardiac intrusion [10].

Although our patient's life was extended for almost 11 months by surgical intervention, good palliation was obtained for only two 3- to 4-month periods, with an intervening second open heart procedure. Because an isolated cardiac metastasis was confirmed at postmortem examination and 1 case of long-term survival after resection of a single pulmonary metastasis has been reported, surgical intervention for patients with metastatic cystosarcoma phyllodes cannot be ruled out entirely. However, patients with the potential for long-term palliation or cure will be extremely rare.

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Intracavitary Melanoma of the Left Atrium

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A 32-year-old man was seen with shortness of breath and increasing fatigue. Echocardiography revealed an intracavitary mass occupying the entire left atrium. The lesion was resected using cardiopulmonary bypass and found to be a large malignant melanoma. This case represents the rare occasion in which antemortem diagnosis of malignant melanoma within left atrium permitted successful palliative surgical resection. The patient is alive and active 6 months after operation.

(Ann Thorac Surg 1990;49:312–3)

Infrequently, the heart is the site of primary or secondary tumors. Primary tumors of the heart are rare and occur with a frequency of less than 0.1% [1]. Metastatic heart tumors are 20 to 40 times more common, with a frequency of 1.5% to 21% reported at autopsy [1, 2]. With the exception of malignant melanoma, no particular tumor has a predilection for metastasis to the heart. This tumor has been reported to involve the myocardium in more than 50% of patients with known melanoma elsewhere. It is most frequently seen as a diffuse intramyocardial process. In this report, we present the case of a young man with intracavitary malignant melanoma involving the left atrium.

In January 1989, a 32-year-old man was admitted to Roswell Park Memorial Institute with the chief complaints of cough, fatigue, and exertional dyspnea. Chest roentgenogram showed bilateral pulmonary lesions consistent with metastatic disease (Fig 1).

In 1984 the patient had undergone excision of a small right submandibular mass that was reported as metastatic melanoma. A primary site was not identified. Six weeks later, a right radical neck dissection for melanoma was performed; the nodes were free of tumor. The patient refused further therapy and was lost to follow-up shortly thereafter.

On this admission, physical examination showed a temperature of 38.9°C, pulse rate of 100 beats per minute, respiration of 18 per minute, and blood pressure of 120/60 mm Hg. The chest was clear to auscultation, the heart rate was regular, and the abdomen was free of masses. Laboratory studies revealed a hemoglobin level of 10.3 g/dL and a white blood cell count of 15,900/mL, with a marked shift to the left. The chemistry profile was normal with the exception of an elevated alkaline phosphatase level (145 U); the patient had a normal electrocardiogram. Because he was febrile with a leukocytosis and was a known intravenous drug abuser, the diagnosis of acute valvular endocarditis was entertained. Two-dimensional echocardiogram revealed a large echogenic mass completely occupying the left atrium (Fig 2). The patient was referred to the cardiothoracic surgery service for tumor excision and relief of symptoms. Intraoperatively, a large pedunculated melanotic mass in the left atrium was identified and removed completely with use of cardiopulmonary bypass. His postoperative recovery was uneventful, and he was discharged 2 weeks after operation. Histological examination confirmed the diagnosis of malignant melanoma. At 6-month follow-up, postoperative two-dimensional echocardiogram showed a normal-sized left atrium, and the patient was free of symptoms. He is currently undergoing interleukin-2/lymphokine-activated killer cell therapy.

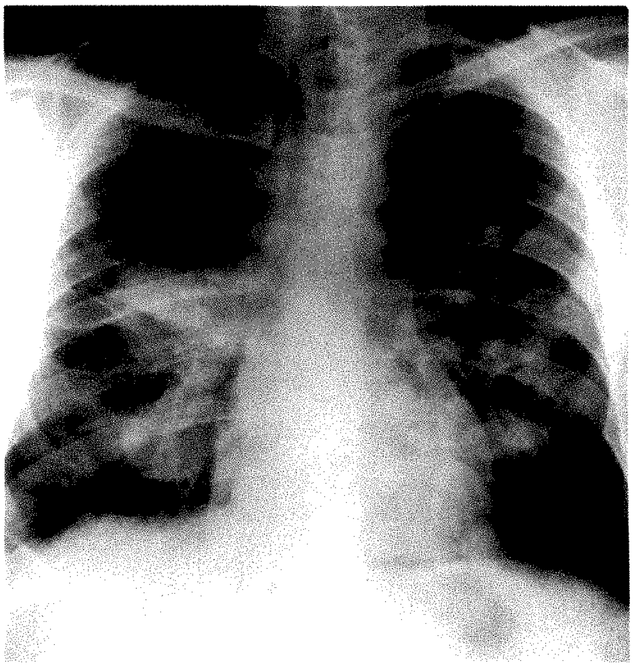

Fig 1. Chest roentgenogram shows bilateral pulmonary metastatic lesions.

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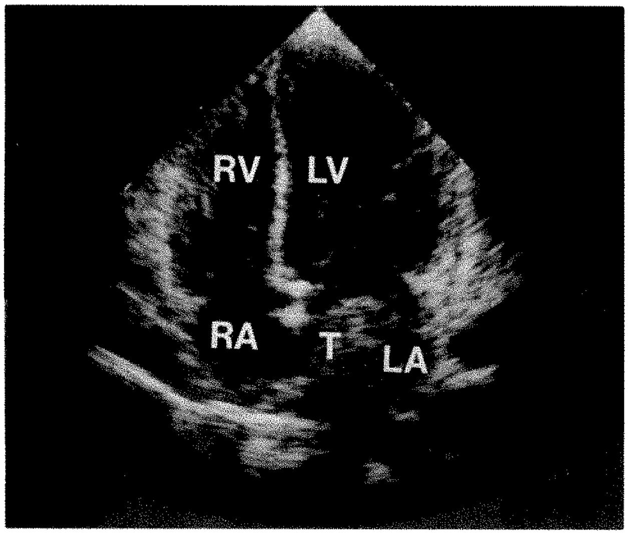

*Fig 2. Apical four-chamber view of two-dimensional echocardiogram shows a large echogenic mass (*T*) in the left atrium (*LA*). (*LV*) = left ventricle;* RA *= right atrium;* RV *= right ventricle.)*

Comment

Although cardiac metastases are frequently associated with systemic tumor dissemination, isolated metastatic tumor limited to the heart is rare. Metastatic tumors presumably reach the heart by hematogenous spread, lymphatic spread, or direct invasion (in descending order of frequency). Malignant melanoma has the highest frequency of cardiac involvement, occurring in as many as 64% of patients with known melanoma [2].

Symptomatic cardiac metastasis from malignant melanoma is a rare occurrence. Recognition of cardiac melanoma is dependent on one's awareness of the probability of occurrence and its diverse manner of presentation. Depending on the location of the melanoma, a variety of manifestations may suggest cardiac involvement. Waller and colleagues [3] suggested that in any patient with melanoma without previously known cardiac disease development of one or more of the following suggests cardiac metastasis: (1) acute pericarditis, (2) pericardial effusion or rapid increase in cardiac size on chest roentgenogram, (3) cardiac tamponade or constriction, (4) atrial tachycardia, (5) second- or third-degree atrioventricular block, or (6) congestive heart failure.

Early detection of metastatic cardiac melanoma has important therapeutic and prognostic implications, although such involvement may be difficult to diagnose clinically. Echocardiography (especially two-dimensional), radionuclide imaging of the heart, magnetic resonance imaging, and radiographic computed tomographic scanning may facilitate identification of metastatic cardiac invasion.

Malignant melanoma of the heart usually involves the pericardium and myocardium and rarely involves the valves or endocardium. On rare occasions, such involvement may be the first and only expression of a remote primary melanoma. Extensive cardiac infiltration by melanoma (charcoal heart), often macroscopic, is most often seen in patients dying of malignant melanoma [3]. Direct invasion of the heart through the venae cavae or pulmonary veins can produce an intracavitary tumor mass, resulting in flow or valvular obstruction. We found only 6 reported cases of intracavitary cardiac melanoma, which can progressively obliterate the left ventricle [4, 5] or both ventricles [6] and may cause right ventricular inflow and outflow obstruction [7, 8]. To our knowledge, no cases of isolated intracavitary metastatic cardiac melanoma to the left atrium have been previously described, however.

This case represents one of the rare situations in which antemortem diagnosis of intracardiac melanoma provided the opportunity for surgical excision, with substantial palliative relief of symptoms.

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Surgical Ablation for Idiopathic Ventricular Tachycardia

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A 33-year-old man with a right-bundle branch, left-axis deviation ventricular tachycardia was medically treated unsuccessfully. Surgical mapping and ablation was performed with a successful surgical result. A discussion of surgical results for this problem is provided.

(Ann Thorac Surg 1990;49:314–6)

Nearly 25% of patients with ventricular tachycardia do not have any form of ischemic heart disease [1]. The known causes of this problem include right ventricular dysplasia, cardiomyopathy, congenital prolongation of the QT interval, and cardiac tumors; it can also occur in patients with "structurally normal" hearts [1–7]. Further review of these "normal" hearts by other investigators suggests that this group of patients has some form of cellular hypertrophy, fibrosis, degenerative changes, or possibly myocarditis [8]. This group is probably best classified as patients having a primary form of electrical disease or idiopathic ventricular tachycardia. Because most patients with idiopathic ventricular tachycardia are effectively treated by medication, very few have had successful surgical ablation. This report is a case study of a patient referred for surgical ablation because of refractoriness to medication for a period of 14 years.

A 33-year-old man was admitted to Loyola Medical center in March 1987 with a 12-year history of wide complex tachycardia. Initially, this patient was believed to have a supraventricular tachycardia and was treated with digoxin and verapamil; neither suppressed the tachycardia. Empirical trials of quinidine and amiodarone therapy were then tried for what was recognized as a wide complex ventricular tachycardia, but neither was effective or tolerated. Ultimately, he was placed on Procan SR (procainamide hydrochloride) with dosages up to 8 g daily after an electrophysiological study at another institution. In 1984, he began to show symptoms of Procan-induced lupus, including pericarditis, arthritis, markedly elevated antinuclear antibody levels, and a positive direct Coombs test. He was treated intermittently with steroids and Indocin (indomethacin) for his pericarditis.

During the 6 months before his admission to Loyola, he had three episodes of sustained ventricular tachycardia while on Procan SR therapy. Each episode had a uniform right-bundle branch block with marked left-axis deviation morphology. Electrophysiological testing at Loyola revealed an easily inducible tachycardia confirmed to be ventricular in origin and having characteristics of right-bundle branch block and left-axis deviation. Flecainide therapy resulted in a complete suppression of the tachycardia during repeat programmed stimulation. Normal coronary arteries and a left ventricular ejection fraction of 48% were seen on cardiac catheterization. Myocardial biopsy demonstrated slight cellular hypertrophy with minimal fibrosis and no evidence of inflammatory infiltrates.

The patient was discharged on a regimen of flecainide and did well for several months; however, an intolerance to the drug including visual disturbances developed. Administration of encainide was then started, but the tachycardia was still inducible during an electrophysiological study. Surgical ablation was then offered as an alternative.

Intraoperative mapping was done with the Bard computerized system (Fig 1). Epicardial mapping revealed an early site of breakthrough at the posterior apex of the heart. After a small lateral apical ventriculotomy, endocardial mapping using a clockwise approach beginning at the apex was done at three levels (36 sites) and demonstrated the site of origination to be the posterior papillary muscle. Cryoablation was performed for three minutes at –70°C at the papillary muscle base of the warm beating heart. Ventricular tachycardia could no longer be induced in the operating room. Despite this noninducibility, defibrillator patches and electrodes were placed. A postoperative electrophysiological study done seven days later showed that ventricular tachycardia could not be stimulated. Follow-up after 6 months revealed the patient to be free of ventricular tachycardia on no medication.

Comment

Although this patient had an anatomically normal-appearing heart with normal coronary anatomy, a biopsy of his heart muscle revealed hypertrophy with minimal fibrosis. This is consistent with the group of patients at the Mayo Clinic who had hypertrophy, fibrosis, degenerative change, or myocarditis [8]. As the Mayo Clinic group demonstrated, these patients generally respond to medical therapy. Ohe and co-workers [9] also reported findings on 16 patients with a right bundle and left-axis deviation tachycardia responding excellently to medical therapy. Calcium-channel blockers in particular were effective in suppressing the tachycardia. Our patient had been treated with many medications including calcium-

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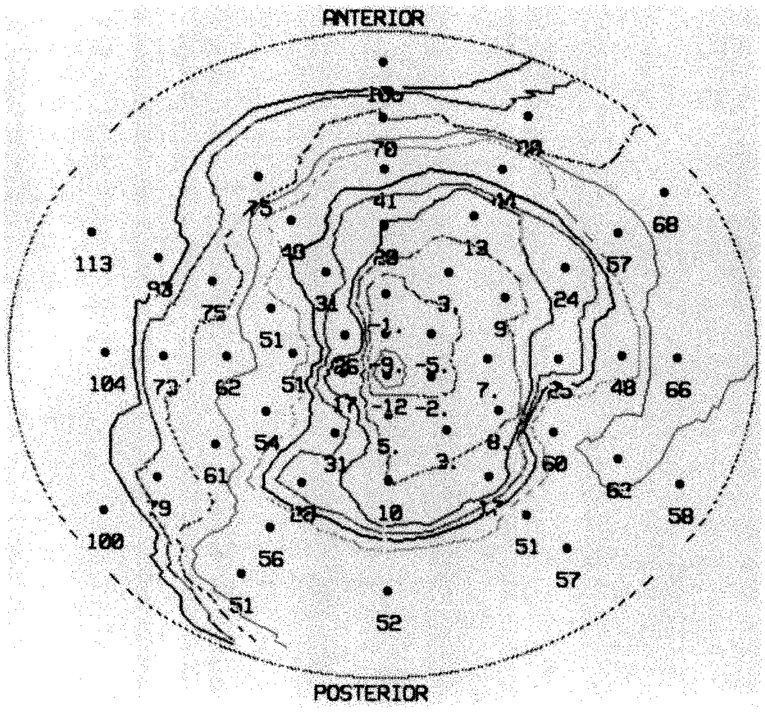

Fig 1. Bard computerized map demonstrating the tachycardia exiting the posterior apex of the heart.

channel blockers but therapy failed due to intolerable side effects of the medication or failure to suppress the tachycardia.

Guiraudon and associates [1] reported 5 patients with idiopathic ventricular tachycardias treated by surgical methods. The basic method used was to place a ventriculotomy at a critical point to interrupt the reentry circuit. The surgical results were not consistently good using this method. Cryoablation using newer devices (Frigitronics) leaves a sharply demarcated injury that has not been demonstrated to be arrhythmogenic, and is probably the treatment of choice for this type of tachycardia [10]. Because no scar was found in our patient, cryoablation was the ablation method used. The French group also noted a higher incidence of failure to interrupt the tachycardia with a septal origin of the arrythmia. Fortunately, our patient's tachycardia was mapped to the posterior apex epicardially and the base of the posterior papillary muscle endocardially. The method of mapping and surgical ablation with a warm beating heart has markedly improved our results for ischemic and nonischemic ventricular tachycardias. A similar result was noted by the University of Virginia team of electrophysiologists and surgeons [11]. This method allows the heart to be remapped and to undergo more cryoablation if necessary.

The question that continues to confuse the issue is whether idiopathic ventricular tachycardia represents an early form of cardiomyopathy. The histological finding in our patient and in the group of Mayo Clinic patients might suggest an early form of cardiomyopathy [8]. Ohe and co-workers [9] did not report the biopsy results of their patients. Only by following these patients over a period of time will the answer be known. Because of this issue and because of the known multiple morphologies of ventricular tachycardia present in some cardiomyopathy patients, the decision to leave defibrillator patches in place was made. This was further justified because the patient was syncopal due to ventricular tachycardia and had failed rigorous courses of medical treatment. Thus, in the future, should other ventricular tachycardia morphologies secondary to cardiomyopathy develop in patients, an implantable defibrillator generator could be easily inserted.

In conclusion, patients with idiopathic ventricular tachycardias who have failed conventional medical therapy and have a monomorphic ventricular tachycardia can be offered surgical ablation as a means of therapy. With improved methods of computerized mapping and cryoablation, and with a better understanding of these patients from the few surgical reports, reasonable results can be expected, particularly when the arrhythmia does not originate in the septum. Implantable defibrillators or antitachycardia pacers will also be available should surgical ablation fail.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 3, 1991. The closing date for registration is August 1, 1990.

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Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Chiari Network Entrapment of Thromboemboli: Congenital Inferior Vena Cava Filter

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Pulmonary emboli and a right atrial thrombus enmeshed in a Chiari network developed concurrently in a 69-year-old man. The network perhaps functioned as an inferior vena cava filter preventing massive pulmonary embolus. Chiari network should be considered in the differential diagnosis of a right atrial mass and the presence of pulmonary emboli should suggest surgical removal.

(Ann Thorac Surg 1990;49:317–8)

Chiari networks are present in 1.5% to 3.0% of hearts at routine autopsy [1, 2]. Only occasionally are these networks clinically significant, and then usually in the pediatric age group [1–8]. We report a case in which a large thromboembolism was trapped in a Chiari network that was identified noninvasively and treated surgically.

A 69-year-old man with controlled hypertension was admitted having sudden onset of palpitations and dyspnea without chest pain. He denied alcohol or tobacco use, and systems review was unremarkable. Physical examination revealed jugular venous distention, irregularly irregular cardiac rhythm with a rapid rate, blood pressure of 150/90 mm Hg, a grade 1/6 systolic ejection murmur, decreased breath sounds at right lung base, and ankle edema. Chest roentgenogram showed an enlarged cardiac silhouette and pulmonary edema. Electrocardiography revealed atrial fibrillation with a ventricular rate of 140 beats/min. Levels of electrolytes, arterial blood gases, and cardiac enzymes were normal. Initial echocardiogram showed normal chamber dimensions with global left ventricular hypokinesis (shortening fraction, 28%). The right atrium was remarkable only for a linear echo that appeared between the intraatrial septum and lateral atrial wall (Fig 1A). The patient was treated with digoxin and furosemide (Lasix), resulting in a prompt reduction of ventricular rate and symptomatic improvement. He was discharged four days later.

On a follow-up echocardiogram 3 weeks later, a gelatinous-appearing mass 2.5 cm in diameter was noted in the lower third of the right atrium. It was attached to the atrial septum, to the lateral atrial wall, and to the linear echoes previously described. The echocardiographic findings were consistent with an atrial thrombus (Fig 1B). The patient was therefore readmitted and heparinized. Ventilation-perfusion lung scan revealed a high probability of emboli to the left lateral base. Cardiac catheterization, done before operation in view of the patient's age, revealed high-grade stenosis of the proximal dominant right coronary artery. Because of the size and mobile appearance of the right atrial mass and evidence of recent pulmonary emboli, surgical intervention was elected. Using cardiopulmonary bypass, a 3 × 2 × 2-cm organized thrombus found enmeshed in the lacelike remnants of the eustachian valve (Chiari network) was removed (Fig 2) and the right coronary artery stenosis was bypassed. Postoperative atrial and ventricular tachyarrhythmias were treated with procainamide and digoxin. The patient was discharged in sinus rhythm, on a regimen of warfarin, after venography demonstrated left-leg, deep-venous thrombosis. It was believed that the right atrial thrombus may have originated from the left leg.

Comment

The right venous valve is formed as the right and left horns of the sinus venosus invaginate. It is usually resorbed, leaving remnants represented by the crista terminalis superiorly and the valves of the inferior vena cava (eustachian) and coronary sinus (thebesian) inferiorly. Rarely, the right venous valve is not resorbed, dividing the right atrium partially or wholly into two, "cor triatriatum dextrum." Chiari network represents incomplete venous valve resorption and results in a reticular network of fine strands attached to the crista terminalis, eustachian, and thebesian valves. Although it has been recognized as an anatomical variant for 75 years, only recently has the use of echocardiography allowed recognition of the network or its associated complications on an ante mortem basis [2, 3].

Chiari network is rarely significant clinically in the adult [3, 4]. It can be the site of thrombus formation causing tricuspid and right ventricular obstruction [5], the presence of a right atrial catheter being a predisposing factor [1]. Postmortem reports have demonstrated that the reticular network may trap thromboemboli originating in the peripheral venous circulation [6, 7]. Chiari network has been associated with cardiac arrhythmias that resolve after removal of the malformation [8].

We have been unable to find other cases of antemortem demonstration of embolic entrapment by a Chiari network. This congenital inferior vena cava filter most likely prevented massive pulmonary embolism. The echocardiographic findings facilitated orderly surgical excision of the mass and coronary artery bypass graft placement. Operation was also associated with resolution of the atrial

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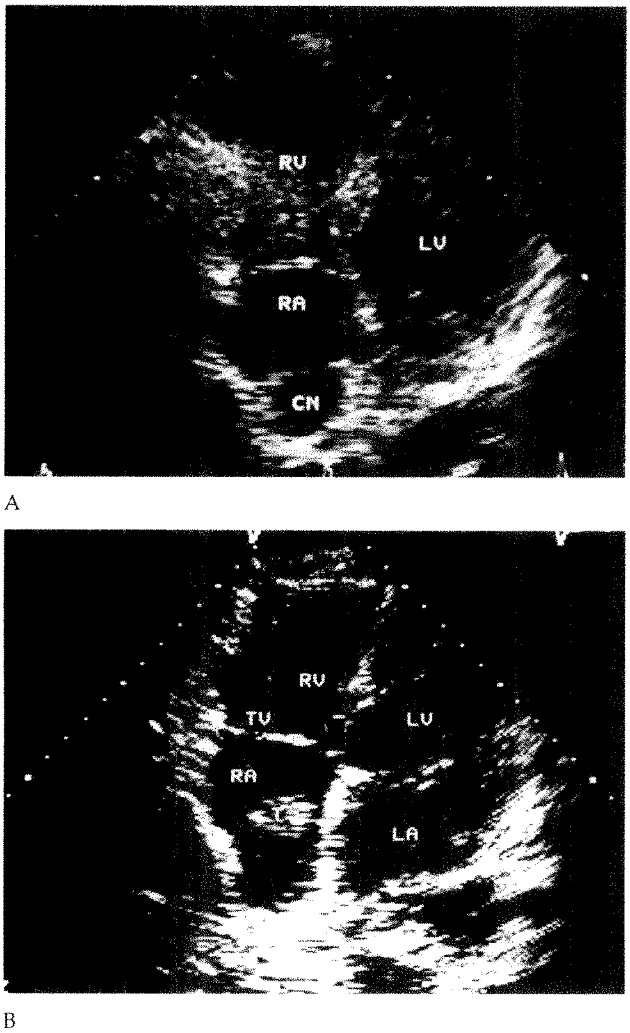

Fig 1. (A) Apical two-chamber view from the initial echocardiogram. Seen within the right atrium (RA) *is a linear echo that appears to extend from the intraatrial septum to the lateral atrial wall, and represents the Chiari network* (CN). *(B) Apical four-chamber view from the follow-up echocardiogram demonstrating the right atrial thrombus.* (LA = *left atrium;* LV = *left ventricle;* RV = *right ventricle;* T = *thrombus;* TV = *tricuspid valve.)*

arrhythmia. Chiari network should be considered in the differential diagnosis of a right atrial mass in the adult, and its known presence should lead to early removal.

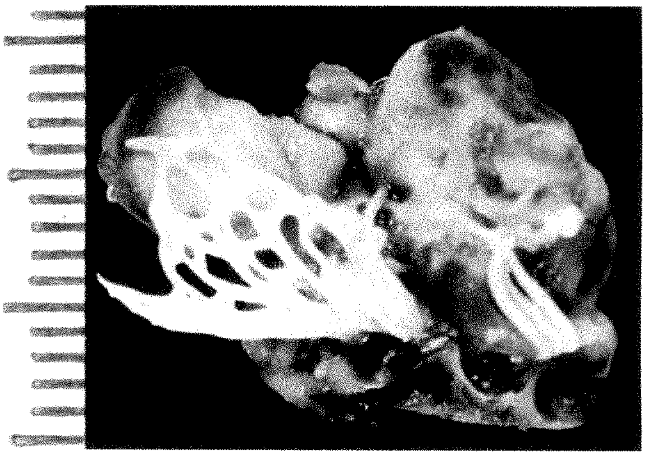

Fig 2. The gross surgical specimen revealing the organized thrombus enmeshed in the Chiari network. One centimeter is equal to the distance between five linear marks on the scale at the left-hand border.

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Group F Streptococcal Empyema From Aspiration of a Grass Inflorescence

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A previously healthy 15-year-old boy was seen with a loculated right lower lobe empyema. Group F β-hemolytic streptococci were cultured from the pleural fluid. Surgical intervention was required. An unsuspected aspirated grass inflorescence and a bronchopleural fistula were discovered during a decortication procedure.

(Ann Thorac Surg 1990;49:319–20)

Lancefield Group F streptococci are part of the normal flora of the mouth, oral pharynx, and gastrointestinal and genitourinary tract [1]. Aspiration of grass inflorescences (seed heads) can result in chronic and bizarre symptoms [2–4]. We describe a case in which a Group F streptococcal empyema resulted from an unreported aspiration of grass.

A 15-year-old boy was seen with a six-day history of pleuritic chest pain, dyspnea, fever, and a nonproductive cough. He had no previous medical problems and gave no history of inhaling a foreign body.

Physical examination revealed a muscular young man with a temperature of 38.6°C. There were diminished breath sounds and dullness to percussion over the posterior right lung. Chest roentgenogram showed a large, right-sided effusion (Fig 1). Thoracentesis fluid revealed 1,550 white cells/μL with 85% polymorphonuclear leukocytes; Gram stain showed no organisms.

Broad-spectrum antibiotics were given. The initial pleural fluid culture grew β-hemolytic group F streptococci. Repeated attempts at closed needle drainage including ultrasonographic directed aspiration failed to substantially reduce the size of the effusion.

A decortication procedure was performed on the fifth hospital day. Exposure of the lung revealed marked inflammation with a fibrous rind overlying the parietal and visceral pleura. There was foul-smelling pus and a hole in the lateral aspect of the right lower lobe consistent with a bronchopleural fistula (Fig 2). A grass inflorescence was found in the lateral costophrenic angle (Fig 3). The portion of right lateral lobe containing the bronchopleural fistula and associated necrotic lung tissue was resected and the decortication was performed. The chest was then closed with adequate chest tube drainage after lavage.

When shown the foreign body, the patient recalled playing a game called "caterpillar" several weeks before admission. This was played by placing the grass inflorescence on the tongue and repeating the word "caterpillar." This causes the inflorescence to move toward the back of the throat. When played with a group, the person who can repeat the word the most times without choking or stopping is the winner. He remembered choking but thought he had coughed out the grass head. He completely recovered.

Comment

The fate of an aspirated inflorescence depends on the botanical characteristics of the grass, with two syndromes as described by Chevalier Jackson [2]: obstruction of a bronchus (lodging type) or perforation of lung tissue (traveling type). Our patient had the latter with the development of a bronchopleural fistula and empyema. Symptoms of pneumonia, hemoptysis, perforation of the lung, and abscess formation have been reported with such aspirations [2–4]. Aspiration of the grass may go unreported.

Group F streptococci are uncommon pathogens with

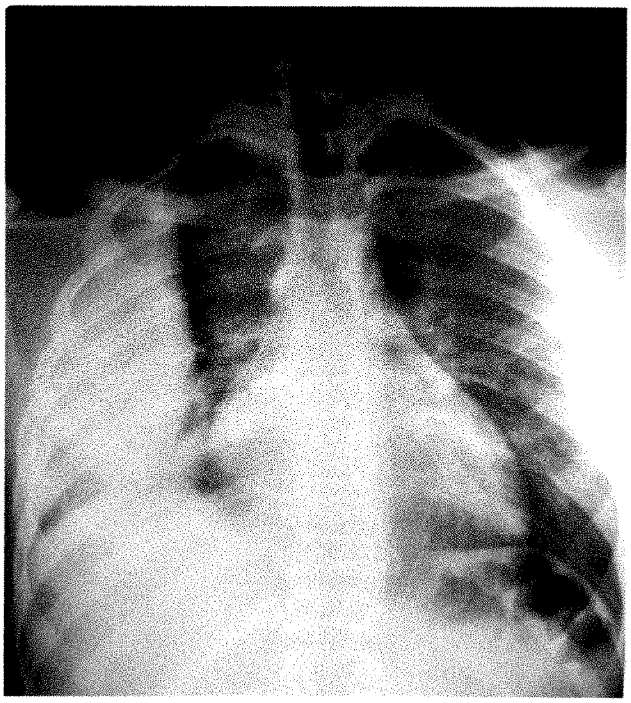

Fig 1. Admission chest roentgenograph showing a large right-sided effusion.

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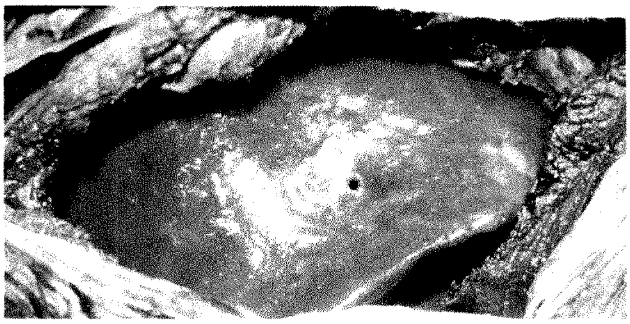

Fig 2. Bronchopleural fistula found at operation.

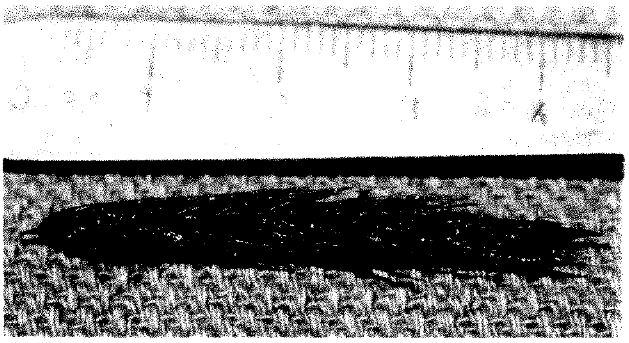

Fig 3. Grass inflorescence found in right costophrenic gutter at time of operation.

the proclivity to form large abscesses [5]. Shlaes and co-workers [6] reported 5 patients with Group F streptococcal empyema who all had a predisposing underlying disease and required surgical decortication. Because our patient was previously in good health, the recovery of the organism was a clue to the unreported aspiration. This case illustrates the importance of considering unanticipated risk factors when confronted with an unusual pathogen.

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Coronary Artery Bypass Grafting With Unanticipated Fibrosing Mediastinitis

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Coronary artery bypass grafting in the setting of superior vena caval obstruction due to unanticipated fibrosing mediastinitis is described. Intraoperative decisions regarding the management of this unusual patient are discussed.

(Ann Thorac Surg 1990;49:321–2)

Although fibrosing mediastinitis is a nonmalignant condition, the proliferation of fibrous tissue within the mediastinum can impinge upon bronchi, cavae, pulmonary arteries, or the esophagus [1–4]. Histoplasma is considered to be the most common cause of fibrosing mediastinitis, although mycobacterial infections, sarcoidosis, nocardiosis, actinomycosis, aspergillosis, syphilis, and idiopathic systemic fibrosis [3–5] have also been implicated. The present case report describes the management of fibrosing mediastinitis and superior vena caval obstruction discovered at the time of elective coronary artery bypass grafting.

A 57-year-old man with unstable class IV angina was referred to the Asheville VA Medical Center for consideration of coronary artery bypass grafting. The patient's history dated to 1981 when he had an acute myocardial infarction. The patient later showed typical anginal symptoms that rapidly worsened over the 6 weeks before admission. Cardiac catheterization showed occlusion of the proximal left anterior descending coronary artery, 95% proximal stenosis of the right coronary artery, and 60% stenosis in the distal circumflex artery. His left ventricular ejection fraction was 78%.

The patient also had chronic pulmonary disease. A right pulmonary nodule and surrounding fibrosis were apparent on chest roentgenogram (Fig 1). This finding had remained unchanged for several years. The arterial blood gas on room air showed a pH of 7.46, carbon dioxide tension of 30 mm Hg, and oxygen tension of 60 mm Hg. On pulmonary function testing, the forced vital capacity was 2.45 L and the forced expiratory volume in one second, 1.02 L. The remainder of the patient's history, physical examination, and review of systems was unremarkable. The patient did not have any symptoms suggesting superior vena caval obstruction. On physical examination, the patient had a ruddy complexion; however, pathological jugular venous distention was not present and the presence of superficial venous collateral vessels over the chest wall was masked by obesity.

At operation, a right internal jugular sheath was placed without difficulty; however, a Swan-Ganz catheter could not be passed into the heart despite multiple attempts. Eventually, the catheter was passed from the femoral vein into the pulmonary artery. Measurements of venous pressure taken from the internal jugular catheter ranged from 3 to 6 mm Hg.

Vigorous venous bleeding was encountered after the skin incision, and upon opening the pericardium, a dense fibrotic mass was seen constricting the superior vena cava. Multiple biopsy specimens of this tissue showed fibrosis and chronic inflammation. No tumor or organisms were seen on multiple sections or with special stains. There was no growth on subsequent culture of the material.

The decision was made to proceed with coronary grafting. The pressure in the internal jugular vein was continuously monitored while the patient was perfused for 60 minutes at a temperature of 25°C. Saphenous vein grafts were constructed to the left anterior descending, first diagonal, and right coronary artery during a 22-minute period of cardioplegic arrest. The patient had an uneventful convalescence without neurological sequelae and has remained angina-free for more than 2 years.

Comment

This patient had no symptoms of superior vena caval obstruction, and his chest wall collaterals were masked by obesity so that the presence of fibrosing mediastinitis compressing the superior vena cava was not diagnosed until the time of operation. Upon diagnosing the obstruction, an effort was made to determine the cause. Examination for fungal and mycobacterial organisms was included in the cultures, and histopathological examination included inspection of multiple sections and the use of a Gomori silver methenamine stain to identify *Histoplasma capsulatum*. Malignancy and mycobacterial infection would require further therapy; however, antifungal drugs have no beneficial effect on established mediastinal fibrosis [6].

In managing a case similar to this, the venous pressure

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in the internal jugular system should be measured before cardiopulmonary bypass is initiated. Presumably, most asymptomatic patients will have well-established venous collaterals and low internal jugular pressure; however, the surgeon must be aware of the potential for impaired cerebral blood flow and brain edema if the patient is perfused with high cerebral venous pressure while in the supine position. If the internal jugular venous pressure is elevated, one can proceed with coronary grafting using an additional venous return catheter placed in the internal jugular vein through a separate cervical incision. However, if the grafting procedure could be safely deferred until a later date, further development of collaterals might make this additional cannulation unnecessary and would, at a minimum, allow optimal positioning and draping of the patient for internal jugular cannulation at the subsequent operation.

Attempts to directly release the superior vena cava from fibrotic encasement are strongly discouraged, although the caseous contents of a large granuloma compressing the cava can be safely evacuated [5]. Other maneuvers to help in maintaining a low internal jugular pressure during bypass would include raising the patient's upper body or conducting perfusion at a sufficiently low temperature to safely allow low perfusion flow during bypass.

If the venous pressure is elevated, a decision regarding permanent bypass of the obstructed superior vena cava must be made. The spiral saphenous vein graft technique as described by Doty [7] is recommended for such a bypass based on previously published results [2, 3, 8].

An aggressive surgical attitude to coronary grafting in the setting of mediastinal fibrosis and superior venal caval obstruction is recommended based not only on the successful outcome in this 1 patient but also on the possible need for other operations in the future [1, 4].

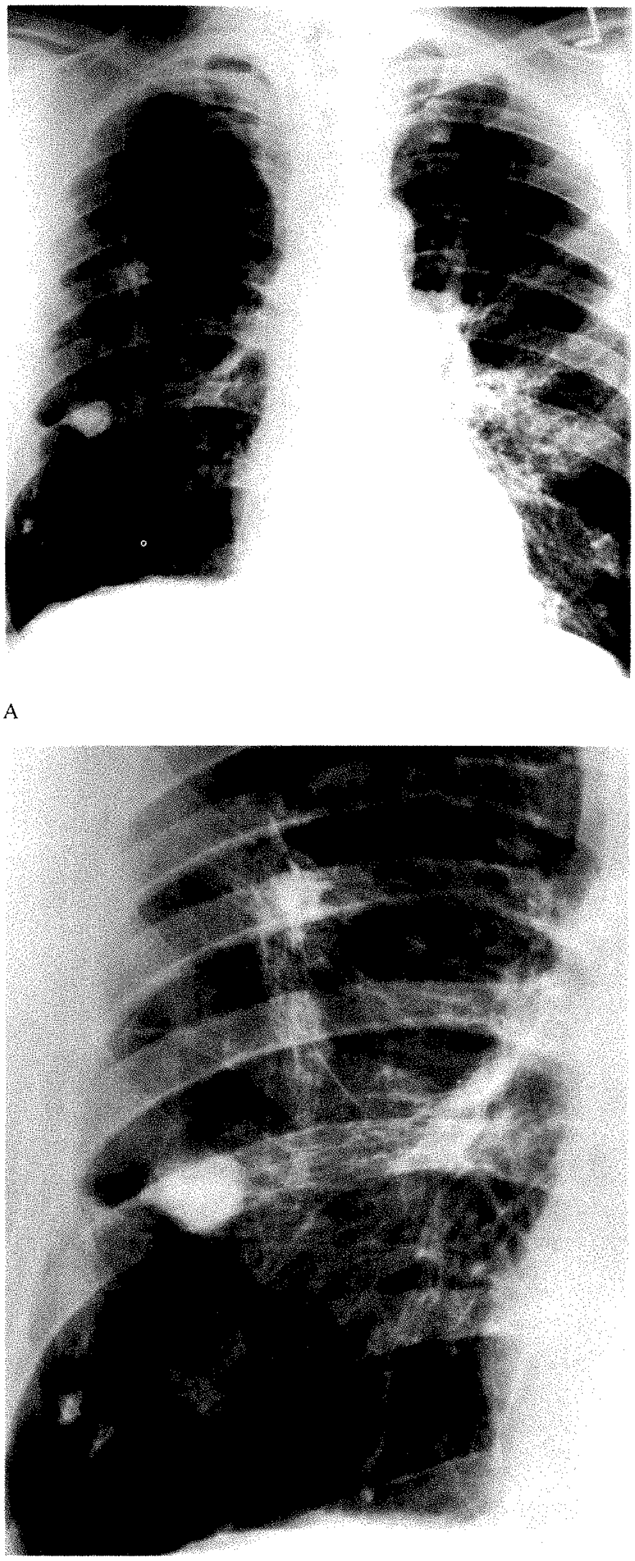

Fig 1. (A) Preoperative chest roentgenogram showing the right pulmonary nodule with surrounding fibrosis. (B) Detail of right lung mass and surrounding fibrosis.

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Inferior Epigastric Artery as a Conduit in Myocardial Revascularization: The Alternative Free Arterial Graft

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When complete revascularization cannot be obtained with the internal mammary artery and greater and lesser saphenous veins, the inferior epigastric artery may be an excellent alternative conduit. We describe our experience with this conduit, review the anatomy of this artery, and present our harvesting technique.

(Ann Thorac Surg 1990;49:323–5)

The internal mammary artery (IMA) has become recognized as the ideal conduit for myocardial revascularization because of its high long-term patency rate, contrasting a high incidence of atherosclerosis of the saphenous vein graft [1]. Despite increased use of bilateral IMA grafts, sequential IMA grafts, and free IMA grafts, additional aortocoronary bypass by means of a venous conduit to ensure complete revascularization is required by the majority of patients. In some patients, contraindications to the use of the IMA do exist; in others, occasions may arise in which the IMA and greater and lesser saphenous veins are unsuitable [2] or unavailable because of various causes. Simultaneously with a considerable increase in the number of reoperations, an increasing need for an alternative conduit is arising, as proved by reports about the use of nonautologous grafts [3]. The recently described use of the right gastroepiploic artery as a pedicle graft to the distal right coronary and circumflex systems may have disadvantages of opening the peritoneal space and creating an additional thoracoabdominal communication [4]. During kidney transplantations, we noticed the attractive caliber and length of the inferior epigastric artery with relation to its potential usefulness as an alternative arterial conduit in coronary bypass grafting. From sheer necessity, we have recently used the inferior epigastric artery in myocardial revascularization in 2 patients and were impressed with the quality of this artery and the relative ease of harvest. In the present report, we review the anatomy and describe a technique of harvesting the inferior epigastric artery.

Method

Anatomy

The inferior epigastric artery arises from the medial side of the external iliac artery just proximal to the inguinal ligament, and at first lies in the midst of the extraperitoneal tissue at the medial side of the abdominal inguinal ring, in intimate relation with the posterior wall of the inguinal canal. The ductus deferens, as it enters the abdomen, hooks around the lateral side of the artery. Accompanied by its satellite veins, the inferior epigastric artery ascends obliquely superiorly and medially toward the umbilicus; after piercing the transversalis fascia, it enters the rectus compartment by passing in front of the linea semicircularis (semilunar fold of Douglas). It then pursues a cephalad vertical course. Grossly demonstrable direct arterial communications between the superior and inferior epigastric arteries may exist in approximately 40% of cases [5].

Technique

A skin incision of approximately 4 cm in length is made over the common femoral artery, 2 cm above and parallel to the inguinal ligament. After incision of the external fascia, the preperitoneal space is entered, and the transitional zone of the external iliac and the common femoral arteries with the origin of the inferior epigastric artery is adequately exposed. Subsequently, if the inferior epigastric artery is of adequate caliber (2 to 3 mm in external diameter), preferentially a paramedian skin incision is made from a level just below the umbilicus to the symphysis, corresponding to the side of the inguinal incision. If a paramedian incision is used, proximity to the midline must be avoided to avoid dehiscence and incisional hernia: incisions in the rectus sheaths should be in the mid-portion of the width of the rectus muscle or slightly more lateral. Alternatively, a midline skin incision can be made and the anterior rectus sheath entered 2 cm from the midline corresponding to the side of the inguinal incision. The midline incision has the advantages of speed and ease of access and avoidance of denervation with muscular weakness and skin numbness. The main disadvantage of this incision, however, is the occasional incidence of incisional hernia.

Subsequently, the rectus muscle is gently freed posteriorly and retracted laterally by an assistant (Fig 1). The inferior epigastric artery and its two satellite veins are identified between the linea semicircularis and the pubic

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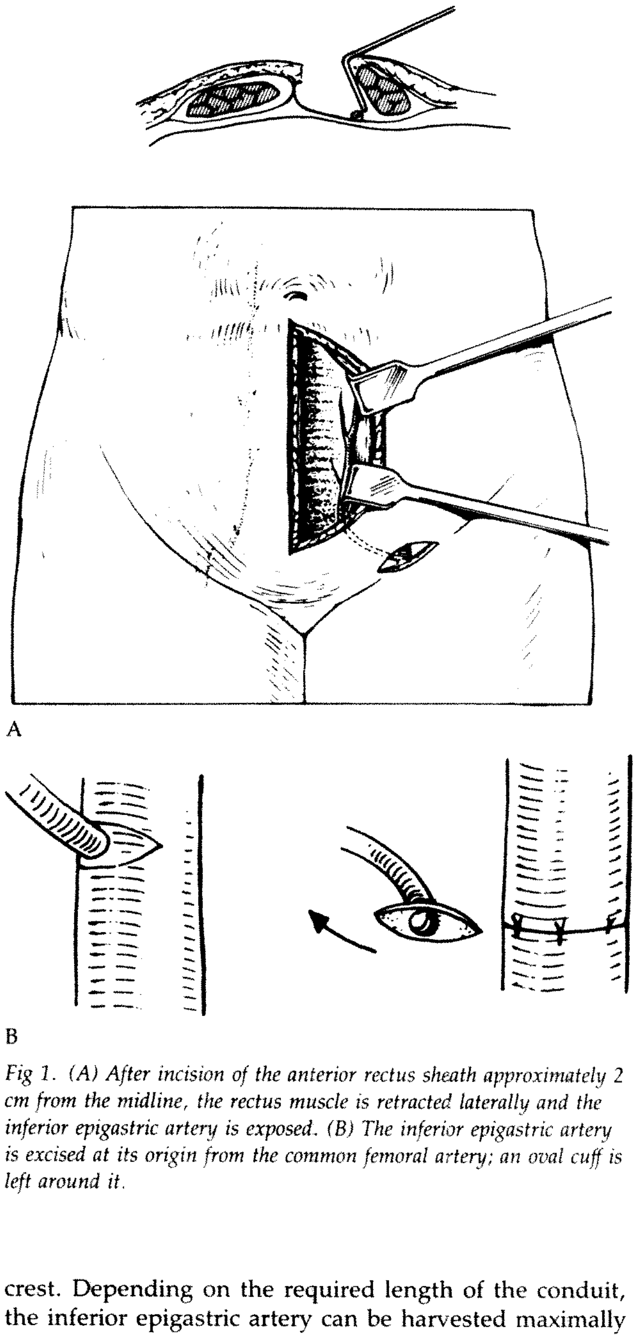

Fig 1. (A) After incision of the anterior rectus sheath approximately 2 cm from the midline, the rectus muscle is retracted laterally and the inferior epigastric artery is exposed. (B) The inferior epigastric artery is excised at its origin from the common femoral artery; an oval cuff is left around it.

crest. Depending on the required length of the conduit, the inferior epigastric artery can be harvested maximally to a level just distal to the umbilicus. Together with its accompanying vein and loose preperitoneal connective and fatty tissue, it is left in a pedicle approximately 2 cm in width to avoid damage from handling. Starting from a point between the origin of the inferior epigastric artery and the umbilicus, the pedicle is further separated from its surrounding loose connective tissue in a proximal and caudad direction using sharp dissection with scissors and electrocautery as well as hemoclips for control of larger branches. The inferior epigastric artery is transversally excised from the common femoral artery with an oval cuff of approximately 4 to 5 mm in diameter to facilitate the anastomosis with the ascending aorta. Subsequently, the proximal part of the inferior epigastric artery is brought to the paramedian or midline incision and the pedicle is transected at its end.

Using this technique, we have been able to harvest free arterial conduits of 20 cm in length. Finally, the inferior epigastric artery is used as a free aortocoronary bypass graft by anastomosing the oval cuff to a punched hole in the ascending aorta and thus creating a naturally tapered origin of the graft.

Comment

The inferior epigastric artery may be a valuable alternative bypass graft when more conventional conduits are absent or unsuitable. Harvesting this artery as described can be accomplished efficiently without entering the peritoneal cavity and with no special instrumentation. It can be harvested simultaneously with the internal mammary artery (and saphenous vein if this is available). We have encountered no detrimental early or late sequelae of the abdominal component of the operation. Necrosis of the rectus abdominis muscle remains a hypothetical risk but was observed in neither of our patients, although in both, the ipsilateral IMA was harvested simultaneously. Also, incisional hernia was not observed. When harvested as described, the inferior epigastric artery can easily reach any portion of the posterior and lateral walls of the heart. In both patients, the grafts were implanted on the second obtuse marginal arteries without any difficulty. The grafts were 17 and 19 cm in length. The harvesting technique of the inferior epigastric artery with its satellite vein in a pedicle is an important issue, as it has been shown both experimentally and clinically that it makes a difference whether a free arterial graft is stripped or is left in a pedicle as described. In the latter situation, the patency rate may approximate that of in situ arterial grafts [6], whereas in the former, a higher incidence of thrombosis, intimal thickening, and medial injury may occur [7].

The patients have been followed for 33 and 27 months after the operation and are in New York Heart Association class I. Although neither has been subjected to postoperative catheterization, we anticipate that the patency of the inferior epigastric artery graft may approximate that of the right gastroepiploic artery graft in spite of creation of an additional proximal anastomosis. This expectation is based on comparative anatomical studies between various arterial conduits as recently performed by us, which showed comparable features of both aforementioned conduits with regard to luminal diameter, morphology of intima, media, and internal elastic lamina, and appearance of vasa vasorum [8].

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In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

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The deadline for submission of applications is July 1, 1990. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Hemorrhage Control After Removal of Surgically Implanted Intraaortic Balloon Pump

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Surgically implanted intraaortic balloon catheters have a substantial potential to cause hemorrhage on percutaneous removal. Because of the unacceptably high incidence of uncontrollable hemorrhage in patients in a life-threatening situation, a new percutaneous surgical modification allowing removal of these balloons with low blood loss has been devised and has proved highly successful in hemorrhage control.

(Ann Thorac Surg 1990;49:326–7)

Most authorities recommend simple percutaneous removal of a percutaneously (Seldinger) inserted intraaortic balloon (IAB) catheter [1], with 30 minutes direct pressure followed by several hours of sand bag and advice to retain the limb in a straight-leg position overnight. There is no provision in this technique for dealing with distal arterial insufficiency; should it occur, the femoral artery must be explored and the circulation reestablished.

Other authorities [2] recommend that when an IAB has been inserted through arterial cut-down onto the supporting femoral artery, regular percutaneous removal is contraindicated and the patient is recommended to have surgical reexploration, explantation, and formal repair.

In the absence of technique modification, there are in my experience several very wise reasons to adopt the latter approach. The preformed surgically created dead-space unable to be obliterated by direct pressure encourages a variable sized hematoma to develop. The patient incurs increasing pain and distress due to the firm pressure over a fresh incision as the hematoma enlarges. Marginal hemodynamics may develop secondary to hypotension from the enlarging hematoma requiring transfusion. Failure to control the situation is frequent and a substantial number of patients will need an urgent operation. The operation to get control is frequently exciting, and I recommend that several units of blood be available for the initial stages of the operation. Opening into the hematoma frequently leads to "audible bleeding" and a great concern of an inability to get control fast enough. Digital pressure is recommended. Should this series of events be avoided by pressure control in the intensive care unit, then in my experience those patients with a large hematoma containing a false aneurysm have an alarming propensity to experience slow dissection superficially over several days, when the hematoma may release in the predischarge ward with dramatic effect.

These patients with surgically implanted IABs thus present a dilemma of hemodynamic instability, a lack of enthusiasm to transport and reoperate, and a desire for minimal invasion but a high serious complication risk for regular percutaneous removal.

As it turned out, this dilemma was relatively easily solved, and surgically implanted IABs are now explanted with use of modified percutaneous techniques that I have developed. At the present time nine IABs have been successfully removed. No pressure is required, no sand bags are required, the surgeon is able to walk away from the bed in less than a minute, and the blood losses have been insignificant. No patient required a reexploration, no hematomas developed, no false aneurysms occurred, no transfusions were required, all patients have been discharged improved, and there have been no infections. Although patients requiring IAB support are prone to experience complications in a general sense, no complications could be ascribed to the modified surgical technique. In 1 patient the intraaortic balloon ruptured during the night and the technique permitted bedside balloon replacement with excellent control of bleeding.

Surgical Technique

The initial effort of IAB insertion is directed to percutaneous femoral artery access. If this is unsuccessful and pulses are not palpable because of obesity, pump flow, peripheral vascular disease, or recent catheterization, and time is pressing, then an oblique incision is made in the groin and deepened to expose the femoral artery.

Through a separate stab incision a Seldinger technique is used to place the intraaortic balloon.

At this point the guidewire is removed and balloon pumping can commence. I now recommend that a 5-0 Gore-Tex (strong with a very low coefficient of friction) pursestring suture be placed about the arterial puncture site. This suture is deliberately left long and is then passed through a red-rubber tourniquet or a similar device. With use of a No. 15 scalpel, an additional stab wound is made away from the IAB skin entry site. Through this new incision a tonsil clamp is passed down to the femoral artery, and one end of the tourniquet is now grasped with the tonsil clamp and brought out through the skin. The deep end of the tourniquet is easily positioned adjacent to the femoral artery puncture site, then the Gore-Tex suture is tightened and secured. (I use two small hemoclips and a plastic spigot; Fig 1.)

When the IAB pump is weaned and no longer required,

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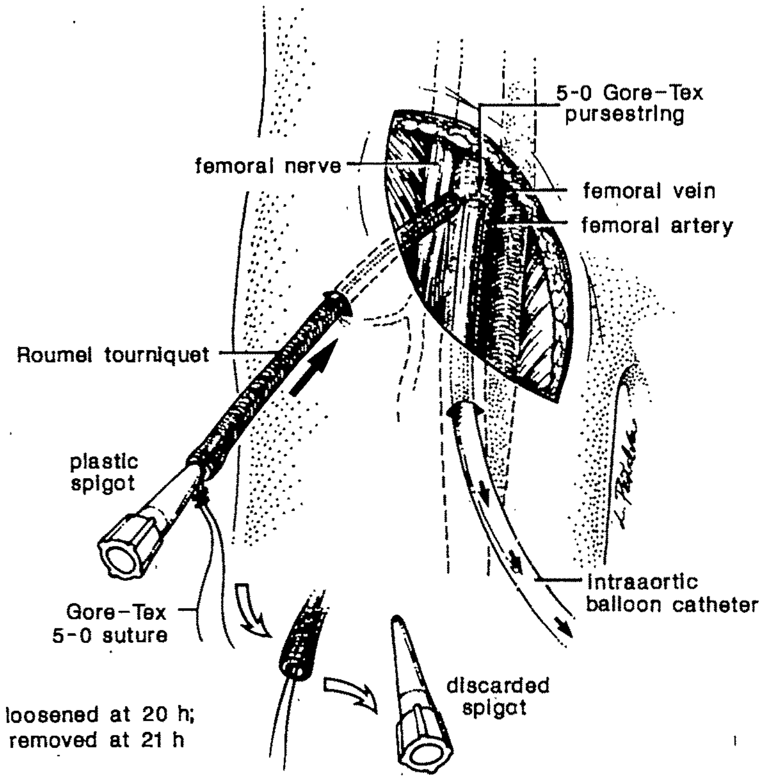

Fig 1. Surgical anatomy and positions of the intraaortic balloon catheter and the rubber tourniquet used to control femoral artery bleeding.

the small hemoclips are removed, the pursestring is loosened, and the IAB is deflated and removed. As the balloon exits the artery, the tourniquet is tightened and left for 16 to 20 hours, after which it is loosened. (I usually leave the tourniquet loose for one hour, but this has been variable.) If there is no bleeding, then one arm of the Gore-Tex suture is cut and both the tourniquet and the Gore-Tex are removed. (Having such a low friction coefficient, the Gore-Tex will slide easily.) Should minor bleeding occur, then it is stopped by local pressure. This has not been a serious problem in this series of 9 patients to date.

Comment

This technique permits percutaneous removal of surgically implanted IABs with low blood loss. There have been no vascular complications; however, if the circulation to the lower leg becomes compromised after IAB removal, then the pursestring should be released. If no improvement occurs, then thrombosis should be suspected and formal exploration carried out.

As recommended, this percutaneous removal technique has reduced the incidence of hemorrhage and other complications from the 13F arteriotomy to 0 in this series of patients and dramatically improved patient comfort after balloon removal.

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C. Walton Lillehei and Total Correction of Tetralogy of Fallot

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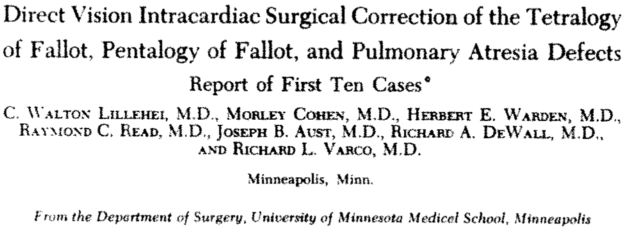
In March 1954, an operating team headed by C. Walton Lillehei introduced the technique of cross circulation for the first-ever total corrections of ventricular septal defect, tetralogy of Fallot, and atrioventricular canal. Ten of 45 patients operated on with this technique of cardiopulmonary bypass had correction of tetralogy of Fallot, and the results with these 10 patients were reported in a landmark article. The operative results achieved in 1954 and 1955 by Lillehei and his team using cross circulation were truly remarkable. In addition, the University of Minnesota team concomitantly developed a host of new techniques and biomedical devices that made subsequent cardiac operative procedures safer and simpler to perform. These techniques and devices included the first ventricular septal defect prosthetic patch, the first right ventricular outflow patch, the first clinically applicable bubble oxygenator, and the first intramyocardial electrode used in combination with an external pacemaker for a patient with complete heart block.

(Ann Thorac Surg 1990;49:328–32)



Direct Vision Intracardiac Surgical Correction of the Tetralogy of Fallot, Pentalogy of Fallot, and Pulmonary Atresia Defects

Report of First Ten Cases*

C. Walton Lillehei, M.D., Morley Cohen, M.D., Herbert E. Warden, M.D., Raymond C. Read, M.D., Joseph B. Aust, M.D., Richard A. DeWall, M.D., and Richard L. Varco, M.D.

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In the early 1950s, an atmosphere of pessimism and discouragement surrounded the possibility of direct-vision repair of complicated intraventricular defects. The late 1930s and early 1940s had ushered in landmark surgical procedures for patent ductus arteriosus, coarctation of the aorta, and tetralogy of Fallot [1–3]. Successful closed mitral commissurotomies by Bailey [4] and Harken and associates [5] in the late 1940s were exciting advances, but by the early 1950s the thoracic surgeon's dream of direct-vision repair of complex intracardiac defects seemed virtually unattainable.

Although F. John Lewis successfully closed an atrial secundum septal defect in a 5-year-old girl using moderate total body hypothermia and inflow stasis on September 2, 1952, at the University of Minnesota [6], his technique was not suitable for the more deliberate repair of ostium primum or ventricular septal defects (VSDs). It appeared that the only feasible approach to these more complicated intracardiac defects was with cardiopulmonary bypass using a pump oxygenator. Using his heart-lung machine at the University of Minnesota, Clarence Dennis had attempted to repair an atrial septal defect in 2 patients in April 1951 [7, 8]. Unfortunately, 1 of these patients was found to have a partial atrioventricular canal, and the pathology at that time was baffling. The second patient who underwent an atrial septal defect secundum repair died of massive air embolism in the operating room. On May 6, 1953, John Gibbon culminated 15 years of intense laboratory research by successfully closing an atrial secundum septal defect in an 18-year-old girl with a screen-type heart-lung machine [9]. This, of course, was a monumental achievement, but four subsequent clinical procedures by Gibbon for the attempted repair of atrial septal defect or ventricular septal defect were unsuccessful and Gibbon was so discouraged that he did not use his pump oxygenator again [10].

Because of the general success of the heart-lung machine in the animal laboratory in the early 1950s but disappointing clinical results, there developed a pessimistic "sick human heart" concept that the malformed human heart with advanced dysfunction and failure could not be successfully opened and repaired without some type of prolonged mechanical cardiac support during the early postoperative period.

Controlled Cross Circulation

It was into this arena of dispirited thoracic surgeons and cardiologists that C. Walton Lillehei brought his team and the radical technique of controlled cross circulation. Between March 26, 1954, and July 19, 1955, 45 critically ill infants and children underwent total correction of a variety of complicated ventricular defects using cross circulation. During this 16-month period, Lillehei and his team were the only surgeons in the world using cross circulation; with it they achieved the first total corrections of ventricular septal defect, tetralogy of Fallot, and atrioventricular canal. Ten of the 45 cross circulation patients had tetralogy of Fallot, and the results with these 10

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patients were reported in the landmark article reproduced at the beginning of this report [11].

The key to the success of cross circulation for open heart repair was twofold. First was the "azygos-flow principle" described by Andreson and Watson [12] and Cohen and Lillehei [13]. These investigators demonstrated that normothermic dogs survived 30-minute periods of complete vena caval occlusion without any sequelae if venous flow continued into the heart through the azygos vein. Under these conditions, Cohen found the average azygos flow to be 8 to 14 mL/min/kg body weight, slightly less than 10% of the normal basal cardiac output. Warden, Cohen, Read, and Lillehei [14] then carried out cross circulation experiments in the canine preparation using three different flows: azygos flow, two-times azygos flow, and three-times azygos flow. They determined that with three-times azygos flow, mean systemic blood pressure ranged between 60 and 80 mm Hg, and that they could perform a ventriculotomy in the canine preparation and then create and suture-close a ventricular septal defect with an overall early survival rate of 71%. Not only did these dogs survive in a much higher percentage, but their recovery was dramatically faster when compared with animals undergoing similar bypass procedures with the high-flow (100 mL/kg body wt/min) pump oxygenators.

The fortuitous discovery of the azygos flow principle provided a number of substantial advantages to Lillehei and his team. The principal new concept demonstrated by the azygos studies was the marked difference between the normal blood perfusion level and the very reduced perfusion level that was actually required for the performance of an open heart procedure. This, of course, greatly simplified the pump and cannula requirements; with a reduced blood flow and coronary sinus return, a clearer view of the complicated intracardiac defects was possible. In fact, the coronary sinus flow was minimal enough that it was discarded during the operative procedure.

The second and equally important bonus of cross circulation was that the donor's vital organs provided automatic and near perfect homeostasis in the patient's system. At that time, there were literally dozens of metabolic derangements occurring that were unknown and thus incapable of management.

After the encouraging cross circulation experiments in the animal laboratory, Lillehei was prepared in the early months of 1954 to take the technique to the operating room in an attempt to totally correct ventricular defects.

Results in 10 Patients Undergoing Total Correction of Tetralogy of Fallot With Cross Circulation

Of Lillehei's first 13 patients undergoing cross circulation, 1 had correction of an infundibular pulmonic stenosis (the suspected VSD was not present) and the remaining 12 had repair of a VSD. The 14th patient, a cyanotic 10-year-old boy referred for a subclavian–pulmonary artery shunt, was operated on on August 31, 1954, for intracardiac correction of a tetralogy of Fallot defect. Using a friend of the family as the cross circulation "donor," the defects were successfully repaired, and that patient is currently alive and leading an active life as a professional musician almost 35 years later. During the next 9 months, 9 additional patients ranging in age from 18 months to 11 years had total correction of tetralogy of Fallot using cross circulation; 1 of the 9 had pulmonary atresia successfully corrected and 1 had a pentalogy defect successfully corrected. Remarkably, 5 of these 10 patients were discharged from the hospital; catheterization of 4 patients showed a complete repair in 2 patients [15], a small residual VSD in the third, and a moderate shunt in the fourth.

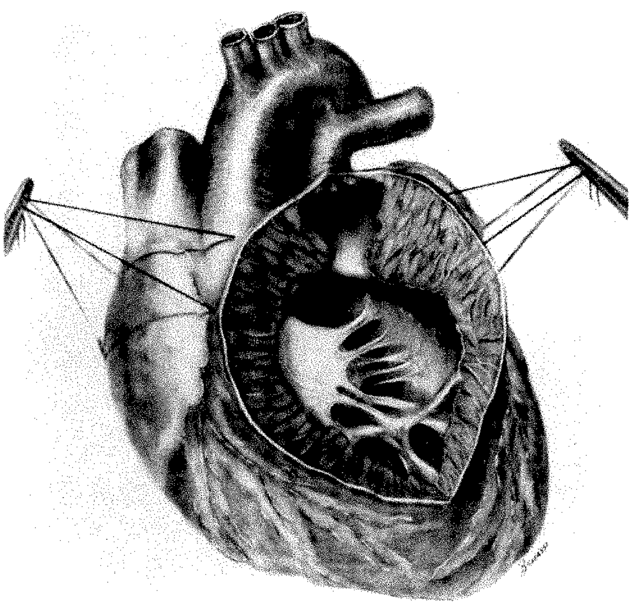

Fig 1. This illustration reprinted from Lillehei's 1955 paper shows the ventricular septal defect and crista supraventricularis as viewed through the right ventricular cardiotomy incision. This illustration was made at the time of the first operation for tetralogy of Fallot repair at the University of Minnesota. (Reprinted from [11] by permission of J.B. Lippincott Co.)

Figures 1 and 2 are illustrations taken from the 1955 paper on the first 10 tetralogy patients by Lillehei and associates [11]. It will be noted that the ventricular septal defect was closed with interrupted 3-0 silk mattress sutures and the crista supraventricularis was resected with a modified Hartmann tonsil punch. The ventriculotomy was closed with a continuous 3-0 silk suture.

Looking back on these early successful corrections of tetralogy of Fallot by Lillehei and his team, there were several remarkable features of the operative procedures. First, the operative times were extremely brief, with the open-heart time ranging between 6 and 21½ minutes. All repairs were carried out on the beating heart, but because cross circulation flows were approximately one-third of the normal basal cardiac output, coronary sinus flow was tolerable. Lillehei and Varco noted that when they placed sutures in the margins of the VSD, particularly in the base of the overriding aorta, distortion of the aortic valve caused flooding of the operative field; therefore, they

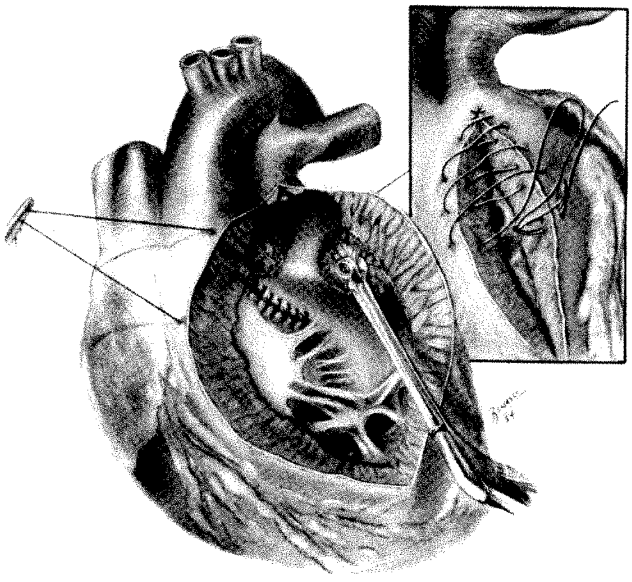

Fig 2. This illustration depicts how the defects shown in Figure 1 were repaired. The ventricular septal defect has been closed with interrupted 3-0 silk sutures and the infundibulectomy is being completed using a modified Hartmann tonsil punch. The inset illustrates the method of closing the right ventricular cardiotomy incision with a continuous 3-0 silk placed in the outer layer of the cut muscle. (Reprinted from [11] by permission of J.B. Lippincott Co.)

employed a Rumel tourniquet clamp with an umbilical tape around the aortic root to permit intermittent occlusion of the ascending aorta.

During the 16-month-period when cross circulation was used for repair of tetralogy, no infant or child at the University of Minnesota Hospital underwent a systemic–pulmonary artery shunt procedure. Lillehei and Varco were prepared to create a shunt if, after opening the pericardium, they believed that total correction could not be achieved. They felt at the time that shunt procedures should be avoided, even in infants, because of potential problems that might occur during subsequent total correction. Prophetically, Lillehei and Varco's preference in 1954 for total correction over the easier shunt procedures foreshadowed the surgical approach to tetralogy that now prevails more than 30 years later.

There were five hospital deaths among the 10 patients with tetralogy operated on using cross circulation. Two of the deaths were considered technical errors; in 1 patient, two of the aortic leaflets were tethered back to the aortic wall by sutures of the VSD closure. A second death occurred because of incomplete closure of a large VSD. The third death resulted from laceration of an anomalous coronary artery in the right ventricular outflow tract area in a patient with adhesive obliteration of the pericardium after an earlier Blalock-Taussig shunt during which the pericardium had been opened for exploration. The remaining two deaths resulted from complete heart block.

It is a tribute to Lillehei and Varco that they were able to close these extremely complicated defects so expeditiously in a relatively wet operative field. Their familiarity with these complex defects was greatly enhanced by their decision 4 years earlier to examine carefully the fresh heart of every patient who died of congenital heart disease at their institution. Hundreds of hours were spent in the autopsy room by these surgeons in the early 1950s examining congenital cardiac defects and practicing the appropriate corrective procedures before formalin had distorted the anatomy.

Lillehei reported his experience with these first 10 patients undergoing tetralogy repair using cross circulation at the American Surgical Association meeting in Philadelphia on April 27, 1955 [11]. Dr Alfred Blalock of Baltimore was the first discussor; he stated, "I must say that I never thought I would live to see the day when this type of operative procedure would be performed. I want to commend Dr. Lillehei and Dr. Varco and their associates for their imagination, their courage and their industry." He added: "The thing that surprised me most about this contribution by Dr. Lillehei is that he seemingly can close a ventricular septal defect where the aorta is overriding this defect. From the many specimens that I saw postmortem, I would not have dreamed that this could have been done because the aorta straddles the defect and there is nothing between the defect and the aorta. So to me, this is perhaps the most important part of their contribution."

Postscript

As an intern on Dr Lillehei's service in March 1954, I had the extraordinary opportunity of observing Dr Lillehei and Dr Varco and their team performing their first cross circulation operation. At that time, Lillehei's achievements with cross circulation seemed absolutely remarkable, but after 35 years, looking back from a perspective of our current high-tech operating rooms and intensive care units, what was achieved in Minneapolis in 1954 seems all the more astonishing. Intraoperative and postoperative monitoring of physiological variables in the cross circulation patients were virtually nonexistent: the only hemodynamic variable monitored invasively was venous pressure; intraarterial pressures were not monitored, and blood gases and pH were not available for clinical practice. Intraoperative and postoperative ventilatory assistance for infants were extremely crude, and pacemakers and external defibrillators did not exist. Thirty years later, Lillehei stated, "Knowing now what we did not know in 1954, it seems very probable that the only method for extracorporeal circulation that could have possibly succeeded so rapidly in the face of such limited knowledge and in the many high-risk infants with complex anatomic lesions was cross circulation. The homeostatic mechanism of the donor automatically corrected the untold number of mostly unknown physiological aberrations evoked by total body perfusion" [16].

During those halcyon days of cross circulation at the University of Minnesota during 1954 and 1955, hundreds of thoracic surgeons from around the world came to Minneapolis to watch Lillehei and his team repair complicated heart defects. One highly respected thoracic surgeon in a half-way serious remark commented to Dr Lillehei that this was the only operative procedure he was aware of that potentially carried a 200% operative mortality.

Because a new field of surgery was being developed by Lillehei and his team at the University of Minnesota in the mid-1950s, a variety of important, new operative techniques and biomedical devices were developed by the group to overcome the new problems encountered each day in the operating room. The first prosthetic patch (compressed polyvinyl sponge-Ivalon) was used to close a large VSD in a tetralogy patient (the 39th cross circulation patient) on April 5, 1955. The first outflow tract roof was used by Lillehei in a tetralogy patient on April 27, 1956. Because of continuing concern about risk to the donor in the cross circulation circuit, there was intense laboratory work by Richard DeWall on a new simple bubble oxygenator, which had its first clinical application on May 13, 1955 [17]. (Again, several hundred surgeons from around the world returned to Minneapolis in 1955 and 1956 to learn more about this new bubble oxygenator that would allow them to return to their medical centers and initiate their own open heart programs.)

Two of the 10 tetralogy patients operated on with cross circulation died of complete heart block. With the therapeutic modalities available in 1954 for the treatment of heart block (epinephrine, atropine, or electrodes applied to the surface of the chest), there were no postoperative survivors in any of the cross circulation patients in whom complete heart block developed. In August 1955, Lillehei began the use of isoproterenol (Isuprel) for surgically induced heart block, and 7 of the next 13 patients with this complication did survive and were discharged from the hospital [18]. Research was carried out in Lillehei's laboratory in 1956 with an intramyocardial electrode connected to an external pacemaker, and on January 30, 1957, the first clinical use of a temporary cardiac pacemaker with an intramyocardial electrode enabled the successful management of complete heart block after tetralogy repair [19]. Seventeen of the next 19 patients with complete heart block treated with the pacemaker were hospital survivors [18].

The late follow-up of these early patients undergoing cross circulation has been summarized in two excellent publications within the last 4 years [16, 18]. In Dr Lillehei's J. Maxwell Chamberlain Memorial Paper presented at the Twenty-first Annual Meeting of The Society of Thoracic Surgeons in January 1985, he provided a 30-year follow-up of the 45 patients undergoing cardiac repair with cross circulation [16]. The reader is strongly urged to read the discussion that followed the presentation of that remarkable paper. Dr John Kirklin, the second surgeon in the world to achieve a series of successful intraventricular repairs beginning March 1955 (using the Gibbon oxygenator) strongly praised Dr Lillehei for his achievements with cross circulation and stated, "I have to conclude that controlled cross circulation was the most physiological technique that has ever been used for cardiac procedures." Dr Denton Cooley, who was also among the first group of surgeons to successfully repair VSDs, closed the discussion with the comment that "Dr. Lillehei's paper not only honors Maxwell Chamberlain, a gifted surgeon and a close friend, but the Chamberlain award recognizes C. Walton Lillehei, a talented investigator and pioneer surgeon who provided the can opener for the largest picnic thoracic surgeons will ever know."

Dr Lillehei's contributions to cross circulation and cardiopulmonary bypass techniques were indeed fortuitous to the development of modern cardiac surgery. Yet, in closing the discussion of the 1955 tetralogy paper that we commemorate here, Dr Lillehei reflected modestly that "The solution of many difficult problems in medicine has ultimately been simple and in most cases obvious once sufficient basic knowledge has been brought to bear on the problem" [11].

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Editor's Note

We asked Dr Lillehei for a response to Dr Gott's interesting article.

Dr Lillehei's Commentary

I am very pleased to have the opportunity to comment on Dr Gott's splendid recounting of the first intracardiac correction of tetralogy defects, which occurred on August 31, 1954.

During the early 1950s the news of the successful advent of open cardiac surgery at the University of Minnesota Hospital in Minneapolis spread rapidly through the medical world, and acted as a powerful magnet attracting young men with some of the best intellects in the world (as it later became evident) to work at the University. Dr Vincent Gott was one of the brightest and best of that select group, who were not only here to receive training, but also, with their innovative ideas, contributed very importantly to the rapid progress that poured forth in those early days.

As Dr Gott has emphasized so well, even as late as the early months of 1954, there were two very important barriers to the achievement of an intracardiac correction of tetralogy. First, there had been no successful use of extracorporeal circulation for simple, not to mention complex, ventricular pathology, although a number of attempts had been made with the pump oxygenator. Second, the universal opinion of interested pathologists and surgeons of that day was that these malformations were too severe to be anatomically correctable.

After March 26, 1954, the successful use of extracorporeal circulation by cross circulation to close ventricular septal defects and to correct the atrioventricularis communis defects overcame that first formidable barrier. Our study of fresh autopsy specimens, in contrast to formalin-fixed specimens, had already convinced me that these defects were readily correctable if they could be visualized. These advances in our knowledge helped to make the first operation we attempted to correct tetralogy the success herein reported.

A few words of recent follow-up on this first patient, M.S., are relevant. Now 35¼ years after his operation, he is 45 years of age. He has been married many years to his childhood sweetheart. Their marriage has been blessed with four normal children. The three oldest boys are now 23, 21, and 18 years of age. Their youngest child is a girl now 15 years old.

They live in a town of 10,000 population that is a computer-component manufacturing and farming center 50 miles west of the Twin Cities. He has been a professional musician since his youth and has his own band, which in 1987 was voted the "Number One Rock and Roll Dance Band in Minnesota." He also runs with his wife an entertainment booking agency.

He remains in excellent health and takes no medications, but his chief health concern, which we have discussed several times, is his inability to quit smoking. He has smoked a pack or more per day for 30 years. He is an intelligent individual, and fully realizes this serious health hazard. He vows "to try again to stop!"

It has been said that mankind has three basic ages: youth, which is looking forward; old age, which is looking back; and middle age, which is looking worried! In that respect it is evident that M.S. has now arrived into the mainstream of a normal "middle age."

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Surgical Management of Heart-Lung Transplantation

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Using cyclosporin A, long-term survival after heart-lung transplantation became possible. The drug blocks the immune system more selectively and leaves the tracheal wound healing unimpaired. Since 1981, 501 clinical cases have been collected by the registry of the International Society for Heart Transplantation. Candidates for heart-lung transplantation reveal signs of irreversible heart and lung diseases that may have been caused by cardiac lesions (valvular diseases, Eisenmenger reaction due to congenital malformations) or by pulmonic disorders (primary pulmonary hypertension, emphysema, fibrosis). The standard surgical procedure, which combines donor and recipient tracheas, right atria, and aortas, makes three anastomoses necessary. Immunosuppressive regimen includes cyclosporin A (blood trough levels of 300 to 500 ng/mL), azathioprine (1 to 2 mg/kg), and rabbit antithymocyte globulin (1 to 4 mg immunoglobulin G/kg). After the first two postoperative weeks, rabbit antithymocyte globulin is replaced by methylprednisolone (0.3 to 0.1 mg/kg; 500 mg are given intravenously after opening the aortic cross-clamp; 3 x 125 mg on postoperative day 1). After heart-lung transplantation an extreme variety of problems may evolve. Early postoperative complications (within the first postoperative month) comprise acute isolated lung rejection, multiorgan failure, and bacterial pneumonia. Diagnosis of acute lung rejection proves difficult; it includes clinical signs, chest radiographic appearances, and cytoimmunological monitoring. Transbronchial lung biopsies are of similar value for precise diagnosis as are endomyocardial specimens after heart transplantation. Late postoperative complications (after 1 postoperative month) comprise viral pneumonia, fungal infection, tuberculosis, and chronic obliterative bronchiolitis. With increasing experience, the 30-day mortality declined to below 20% according to the International Society for Heart Transplantation; 66.5% of the patients who were operated on worldwide between 1986 and 1988 are alive and well after 1 year. The results of some individual groups are even better. In 1989/1990, heart-lung transplantation seems to have become a clinical method with acceptable results. The donor shortage remains a major problem.

(Ann Thorac Surg 1990;49:333–40)

Historical Vignette

The Russian scientist V.P. Demikhov was first to achieve heart-lung transplantation (HLTx) in an animal experiment in October 1946. Later, in 1951, one of his dogs named Damka survived for six days and was then presented to the Russian Academy of Medical Science [1]. Demikhov (Fig 1) did not have a heart-lung machine, and simply used the technique of cross circulation, whereby donor and recipient were connected through the azygos vein and the subclavian artery, respectively.

However, many years of further worldwide investigations were necessary to mold the techniques for clinical application of HLTx (a detailed review is given in reference 2). The discovery of Nakae and co-workers [3] in 1967 that respiration of primates functions without the Hering-Breuer reflex proved an important finding. Five years later, Castaneda and co-workers [4, 5] showed in autotransplantation experiments in baboons that intact phrenic nerves were essential for long-term survival.

Heart-lung transplantation was clinically introduced by Cooley and associates in 1968 [6], followed by Lillehei [7] and Barnard [8] in 1970 and 1971. Although the surgical procedure was technically successful, the outcome of these patients was unfortunately doomed by tracheal dehiscence and consecutive sepsis, sequelae of the then unsophisticated immunosuppression. This has changed since the introduction of cyclosporin A by Borel and colleagues [9]. The drug not only blocks the immune system more selectively, but also leaves wound healing properties unimpaired. Cortisone is not necessary at all or is needed only in smaller dosages.

With cyclosporin A, successful long-term results were achieved at Stanford by Reitz and co-workers, first in the laboratory and then clinically, in 1980 through 1981 [10, 11]. Since then, 501 clinical cases had been collected by the registry of the International Society for Heart Transplantation by the end of April 1989 (Fig 2). Most procedures were performed by Yacoub and colleagues [12] (London), Jamieson and co-workers [13] (Stanford, CA), Griffith and co-workers [14] (Pittsburgh), and Wallwork and English

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Guest Speaker at the Thirty-fifth Annual Meeting of the Southern Thoracic Surgical Association, Marco Island, FL, Nov 10–12, 1988.

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Fig 1. The Russian scientist V. P. Demikhov was an honored guest at the Ninth Meeting of the International Society for Heart Transplantation held in Munich, April 1989, at which he received the Pioneer's Award.

[15] (Cambridge). Our own initial experiences were gained first in Munich and then in Cape Town [16].

Indications and Contraindications of Heart-Lung Transplantation

Indications for HLTx are shown in the following list:

- Primary cardiac disease
  - Pulmonary hypertension secondary to valvular lesions (valvular replacement or repair would usually be considered)
  - Eisenmenger reaction resulting from congenital lesions (cave adhesions resulting from previous interventions)
- Primary pulmonic disease (plus cor pulmonale)
  - Primary pulmonary hypertension
  - Emphysema (bilateral lung transplantation possible [17])
  - Fibrosis (single lung transplantation possible [18])
  - Cystic fibrosis (bilateral lung transplantation possible [17])
  - Multiple pulmonary emboli (thromboendarterectomy might be an alternative [19])
  - Benign lung tumors such as intravascular bronchoalveolar tumors

The 40- to 50-year-old candidates for HLTx show signs of irreversible heart and lung disease, with dyspnea at rest being the leading symptom. Cyanosis and clubbing correlate with the decreased arterial oxygen tension (while the carbon dioxide tension and pH remain normal). Hemoglobin level increases to 18 to 20 g/dL.

Other important organ lesions must be ruled out; nevertheless, kidney and liver function tests are usually slightly abnormal. Patients with irreversible liver damage resulting from long-standing tricuspid incompetence must be excluded, however. Acute infections must also be ruled out and chronic lung infections as well as diabetes mellitus should be well controlled.

During cardiac catheterization, a pulmonary vascular resistance of at least 7 to 8 Wood units is usually documented (in Cape Town, patients with resistances of 5 to 7 Wood units would still be acceptable for heterotopic heart transplantation [20]). The pulmonary artery pressure is at least as high as the systemic pressure, and right ventricular functional variables are impaired.

Preoperative lung function tests prove disappointingly inconclusive: some of the patients have restrictive changes, others may have an obstructive pattern [14, 21]. This discordance is explained by the fact that in candidates for HLTx, the symptoms of right heart failure prevail.

Operative Techniques

Organ Preservation

Before removal of heart and lungs from the donor, verification of their unimpaired function is necessary. The heart should maintain an adequate cardiac output if the peripheral pressure remains stable at a low central venous pressure without catecholamines (dopamine may be administered, however). Lung function is assumed to be adequate if at a fraction of inspired oxygen of 0.4 and an inspiration pressure of maximum 30 cm H_2O the arterial oxygen tension measures at least 100 mm Hg.

Electrocardiograms and chest radiographs are examined carefully. The latter are also used to aim at an accurate size match between donor lungs and recipient thorax. As a general rule, choosing a smaller donor is advisable. (See section on mismatch of donor lung with recipient thorax.) To exclude unknown aspiration, bronchoscopy and Gram stain of the aspirated secretions are performed.

For HLTx, on-site donor procurement may still have an advantage, yet because of the severe organ shortage, long-distance donor procurement is often unavoidable. With one of the clinically accepted methods—cold storage or autoperfusion—safe ischemic times of up to six hours can be achieved [14, 22, 23; see also reviews on lung preservation in 2, 24].

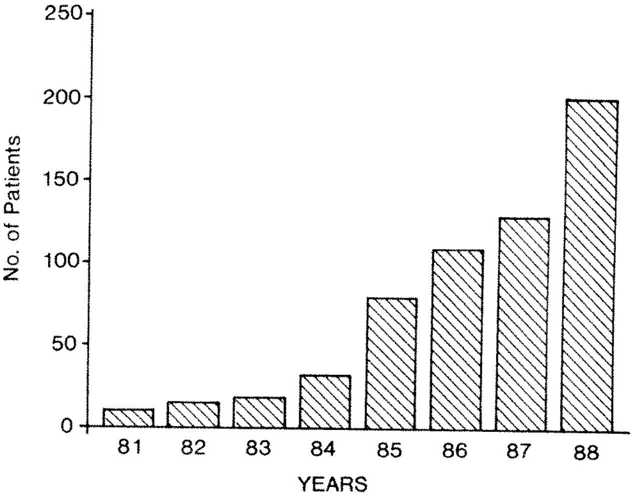

Fig 2. Annual number of heart-lung transplants performed worldwide according to the registry of the International Society for Heart Transplantation (with permission from M. Kaye, San Diego, CA.)

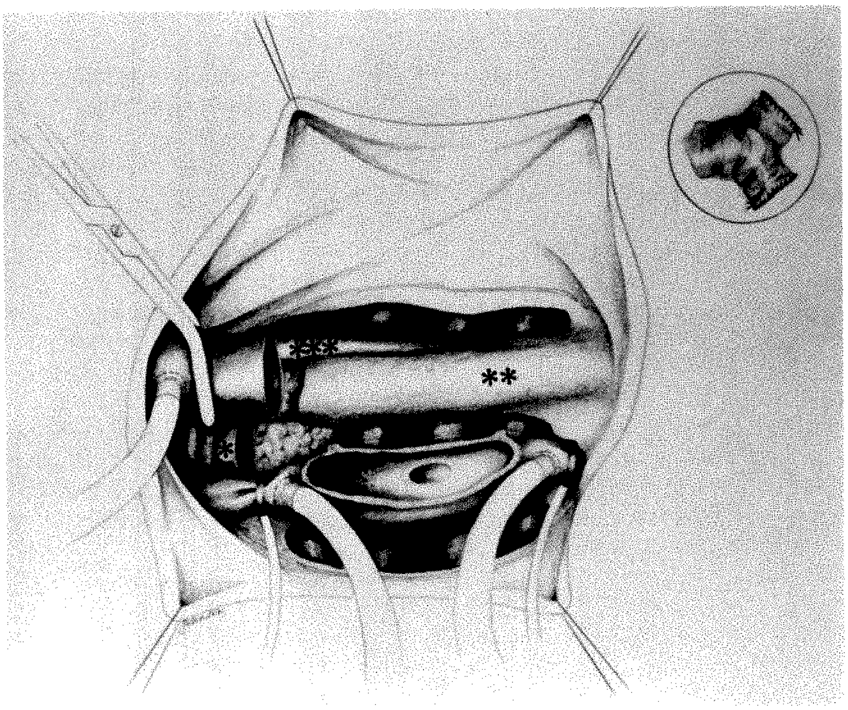

Fig 3. Heart-lung transplantation: operative site (surgeon's view) after median sternotomy has been performed. The heart (as for orthotopic replacement) and both lungs were removed (ascending aorta, superior vena cava, and inferior vena cava are cannulated; the ascending aorta has been cross-clamped). Inset: Resected carina. Two incisions, below the right and the left phrenic nerve, respectively, open the view into the corresponding chest halves. (= tracheal stump, ** = esophagus, *** = descending aorta). (Reproduced from [29] by permission of Springer-Verlag.)*

For cold storage, two different preservation solutions are necessary: a solution for cardioplegia and modified Collins' solution (50 mL of 50% glucose and 12 mEq $MgSO_4$ are added) for the lungs. Some groups of investigators [25, 26] treat the donor before organ harvesting with either prostacyclin or iloprost (20 ng/kg/min). Successful preservation with modified whole blood (to 500 mL blood are added 700 mL Ringer's solution, 100 mL 20% mannitol, and 200 mL salt-poor albumin) was also achieved [27].

Cold preservation is completed by adding topical cooling. For long-distance procurement, the heart and lungs (slightly inflated) are kept in two sterile plastic bags filled with Collins' solution and stored in a cool box filled with crushed ice.

Explantation of the Donor Heart and Lungs for Cold Storage

For explantation of the thoracic organs, a median sternotomy is performed and the frontal part of the pericardium is removed; both pleural cavities are entered. The patient receives heparin (2.5 to 3 mg/kg). The superior vena cava and the azygos vein are doubly ligated and transected. Thereafter, the ascending aorta and the inferior vena cava are cross-clamped, and cardioplegic (20 mL/kg) and modified Collins' solutions (60 mL/kg) are administered through separate 10F cannulas positioned in the aorta and the pulmonary artery trunk, respectively. The fluids are evacuated from the heart chambers through two incisions, into the inferior vena cava and the left atrial appendage. Heart and lungs are then removed from the cranial to caudal direction after the ascending aorta and the trachea are divided (approximately 2 cm above the carina).

Explantation of the Recipient Heart and Lungs and Implantation of the Donor Organs

Because the technique has been described elsewhere in detail [28], we describe it only in brief. After a median sternotomy, heparin is administered; extracorporeal circulation is instituted, with the aortic arch and both cavae cannulated separately. The ascending aorta is cross-clamped, and the recipient's heart is removed as for orthotopic heart transplantation. The remnants of the left atrium are also resected. The surgeon then opens both pleural cavities beneath the sternal borders. Two additional incisions are made 2 to 3 cm below the left and right phrenic nerves, respectively, to facilitate the bilateral pneumonectomies (and the subsequent placement of the donor lungs). The trachea is transected approximately 2 cm above the carina, and the rest of the tracheal bifurcation is removed (Fig 3).

In implanting the thoracic organs, the surgeon gently pushes the left lung through the pleural incision below the left phrenic nerve into the left thoracic cavity. The right lung is guided beneath the remnants of the right atrium and the superior and inferior venae cavae and into the right chest. The implantation is completed by simple 4-0 running polypropylene suture lines, beginning with the trachea, continuing with the right atrium, and finishing at the ascending aorta.

Possible Intraoperative Pitfalls

Persistent Left Superior Vena Cava

The presence of a persistent left superior vena cava draining into the coronary sinus impedes explantation of the thoracic organs considerably, especially that of the left lung. Insertion of a third venous cannula to attach to the extracorporeal circulation is helpful. During removal of the recipient heart, care is taken not to injure the huge coronary sinus by excising the left heart below, at the left ventricular level. The coronary sinus is then dissected from the left atrium as well, thus freeing the anomalous venous return up to its entrance into the pericardial cavity. Drainage into the right (donor) atrium is achieved by connecting the left superior vena cava end-to-end to the (donor) innominate vein, which is deliberately left long [30].

Mismatch of the Donor Lung Within the Recipient Thorax

The necessity of an exact size match between donor lungs and the recipient thorax has been described (see Organ Preservation section). Lungs that are too large could cause symptoms of cardiac tamponade when the sternum is closed. In some cases, final closure must be postponed for a few days, until edematous fluid within the lungs has subsided; provisional chest closure is then achieved by skin suture only or by placing a Silastic sheath between the skin edges. In cases of severe cardiac tamponade, a left upper or lower lobectomy may be life-saving. In contradistinction, lungs that are too small are not detrimental.

Immunosuppressive Therapy

Immunosuppressive treatment consists of a combination of cyclosporin A, antithymocyte globulin, azathioprine, and cortisone. Immediately preoperatively, the recipient is loaded with 3 to 5 mg/kg of oral cyclosporin A and 2 mg/kg of azathioprine intravenously. While the patient is on extracorporeal circulation, antithymocyte globulin (2 to 4 mg of immunoglobulin G/kg) is added intravenously. Before the aortic cross-clamp is released, 500 mg of methylprednisolone is administered, followed by three dosages of 125 mg of methylprednisolone for the first 24 hours after operation.

For the next 2 weeks, rejection prophylaxis consists of a daily combination of oral cyclosporin A (3 to 5 mg/kg; according to blood trough levels <400 ng/mL), azathioprine (2 mg/kg; leukocytes greater than 5,000 cells/μL) and antithymocyte globulin (2 to 4 mg immunoglobulin G/kg; peripheral T cells less than 50/μL). After 14 days, antithymocyte globulin is replaced by oral methylprednisolone (0.3 to 0.15 mg/kg).

Possible Complications During the Early Postoperative Course (Within the First Month)

Reperfusion Damage of the Lungs

Lungs do not tolerate normothermic ischemia for more than 30 minutes [31]. Reperfusion after longer periods disrupts the fine alveolar cell order separating air from blood; consequently, plasma and blood cell components leak into the alveoli and the interalveolar septa.

The term *reperfusion reaction* describes the corresponding, potentially reversible, deterioration of lung function that occurs within the first few days after ischemia [32, 33]. The pathological findings may be aggravated by surgical disruption of the lymphatic, nervous, and bronchial artery supply [34–37].

Reperfusion reaction occurs consistently in experiments using nonprimates; dogs in particular appear not to tolerate any period of ischemia well. The typical chest radiographic appearance that accompanies such a condition is of fluffy opacifications, predominantly around the hilar structures of the lungs [32, 38–40]. Reperfusion reaction of the lungs has, however, also been described in nonhuman primates after normothermic ischemia [41, 42]. If hypothermia is applied, and if the lungs are kept partially inflated, ischemia appears to be tolerated well in primates for up to five hours, and reperfusion reaction is rarely observed [43].

In the clinical setting, where similar techniques are employed, early lung deterioration due to reperfusion reaction is also rare. If it does occur, fluid restriction and vigorous diuresis (even with the help of hemofiltration or dialysis) are mandatory.

Acute Rejection of the Lungs

Of the two thoracic organs, the lungs are rejected more often and earlier (around the fifth postoperative day) than the heart (usually from the seventh postoperative day on [44]). The more pronounced immunogenic reactivity of the lungs may be explained by its richness of lymphocytes (bronchus-associated lymphoid tissue). Prop and coworkers [45] postulate reactions between passenger (donor) lymphocytes and (recipient) cells from the spleen, a reaction similar to that of a mixed lymphocyte culture.

A precise clinical diagnosis of acute, isolated pulmonary rejection is difficult to make. Lung rejection is assumed when at about the fifth postoperative day a sudden increase in temperature (39° to 40°C) occurs. Lung function deteriorates; dyspnea at rest corresponds with a decrease in arterial oxygen tension; the increased lung stiffness (resulting from edema) sometimes makes reintubation and ventilation necessary. Multiple bilateral opacifications are then evident on chest radiograph.

Noninvasive tests confirm the suspicion of acute isolated pulmonary rejection; in our unit, cytoimmunological monitoring of the peripheral blood is used (Fig 4) [46, 47].

Broncheoalveolar lavage was inaugurated by the University of Pittsburgh group [14, 48]. For the procedure, the investigator inserts, with the patient under local anesthesia, a flexible bronchoscope into the area near a big infiltration. The bronchi are then washed; a stained smear from the aspirate is investigated under the light microscope. A percentage increase of both lymphocytes and granulocytes is typical of acute pulmonary rejection.

Repeat transbronchial lung biopsies are of similar value for precise diagnosis of acute pulmonary rejection, as are endomyocardial specimens after heart transplantation [12, 49, 50]. Transbronchial lung biopsies also prove valuable if cytomegalovirus and *Pneumocystis carinii* infections must be excluded. Open lung biopsies are indicated only in life-threatening conditions, when transbronchial techniques have proved unsuccessful.

Treatment of acute pulmonary rejection poses a problem. Ideally, one would like to withhold high dosages of cortisone to ensure unimpaired healing of the tracheal

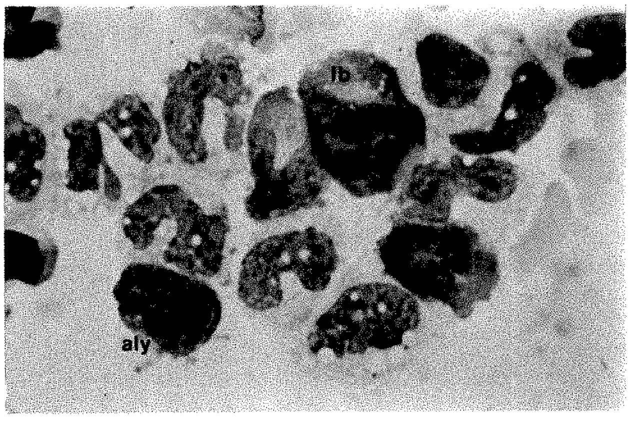

Fig 4. Cytoimmunological monitoring: monolayered smear of the mononuclear concentrate. (Pappenheim stain, ×1,250 before 50% reduction.) (aly = *activated lymphocyte;* lb = *lymphoblast.*)

anastomosis and to prevent opportunistic infections. During the first 2 weeks, intravenous treatment with 1 g of methylprednisolone daily for three days is therefore only started if severe dyspnea is present; at a later postoperative stage an increase in oral methylprednisolone might be sufficient. Administration of OKT3 (5 mg daily) may be considered as an alternative.

Multiorgan Failure

Rapidly progressing and ultimately lethal kidney and liver failure may result from a combination of several damaging factors such as preexisting, chronic renal and hepatic disease, operative trauma, and, finally, nephrotoxicity and hepatotoxicity resulting from drug treatment. Patients with serious preoperative liver disease (serum bilirubin greater than 2.5 mg/dL) therefore should not be considered for HLTx [51].

Bacterial Pneumonia

Early onset of bacterial pneumonia may occur after contaminated lungs have been transplanted. Aspiration before intubation of the donor is then the usual cause. Bronchoscopy and Gram stains are therefore recommended before any explantation is performed.

Possible Complications During the Later Postoperative Course (After the First Month)

Viral, Bacterial, Fungal, and Protozoal Infections

As is true for other organ transplant procedures, most patients die from infectious causes (a review of the most common infections is given in references 2, 52–56). Heart-lung transplant patients are prone to pneumonias, especially to those caused by opportunistic organisms such as cytomegalovirus [57] and *P carinii*. Because both infections carry a high mortality, prophylaxis is advisable: cytomegalovirus-negative recipients ideally should receive organs only from seronegative donors, as Wreghitt and co-workers [58] verified an increased risk of infection if such patients receive cytomegalovirus-positive organs. When a severe organ shortage exists, however, ideal conditions are virtually impossible. Seronegative patients should therefore receive cytomegalovirus hyperimmune γ-globulin (Cytotect) prophylaxis [59]. Furthermore, careful dosage of methylprednisolone appears to be important.

Florid cytomegalovirus pneumonias are treated with guancyclovir (dihydroxy-propoxymethyl-guanin, 10 mg/kg) [60, 61] or with hyperimmune γ-globulin. *Pneumocystis carinii* infections may be avoided by prophylactic administration of trimethoprim/sulfamethoxazole (double-strength tablets of Bactrim twice daily) [62].

Chronic Obliterative Bronchiolitis

Chronic obliterative bronchiolitis has proved to be one of the main obstacles after HLTx. Burke and co-workers [63] diagnosed this complication in 41% of their patients, on the average 14.1 months after transplantation. In a more recent publication, Scott and co-workers [64] reported that this late complication developed in 5 of their 47 patients (10.6%), with three deaths 11, 14, and 33 months postoperatively. (The latter group's lower rate of obliterative bronchiolitis may be partially explained by its more liberal handling of the indication for transbronchial lung biopsies, followed by immediate and aggressive therapy.)

A multitude of etiological factors may be responsible for obliterative bronchiolitis after HLTx, such as obstructed lymph drainage, irreversible denervation, infections (caused by cytomegalovirus, *P carinii*, or Epstein-Barr virus [65]), and continuing pulmonary rejection episodes; the latter is likely to be the dominant injury [64, 66, 67].

Symptoms of obliterative bronchiolitis include progressive breathlessness, dry, unproductive cough, and fever (up to 39° to 40°C). On auscultation, expiratory rhonchi are present. The chest radiograph may reveal basal dominant, honeycomb-shaped shadows.

During the early stages of obliterative bronchiolitis, endobronchial biopsies reveal ulcerations of the bronchial mucosa. Mucous plugs fill the bronchial lumen almost completely; necrotic epithelial cells, granulocytes, and macrophages are found. Later, the exudate becomes organized. Granulation tissue forms typical onion-shaped layers and is covered with a thin bronchial epithelium; squamous metaplasia is frequent.

During the chronic stage, extensive subepithelial scar tissue is found, protruding partially through the basal membrane into the muscular layer. As a result, the bronchial lumen becomes rigidly constricted (Fig 5) [68].

When one is confronted with the problem of obliterative bronchiolitis, an intensive search for pulmonary infections is recommended first. This makes bronchoscopy necessary, and transbronchial lung biopsy is usually performed simultaneously. During lung function tests, airway conductance and mean forced expiratory flow during the middle half of the forced vital capacity are deteriorated [21].

With the diagnosis confirmed, early obliterative bronchiolitis should be treated intensively, the main objective being prevention of possible infections. Regression of the clinical changes have been described if augmented immunosuppression is performed early and aggressively. If the disease of obliterative bronchiolitis is far advanced, however, these therapeutic steps are no longer effective.

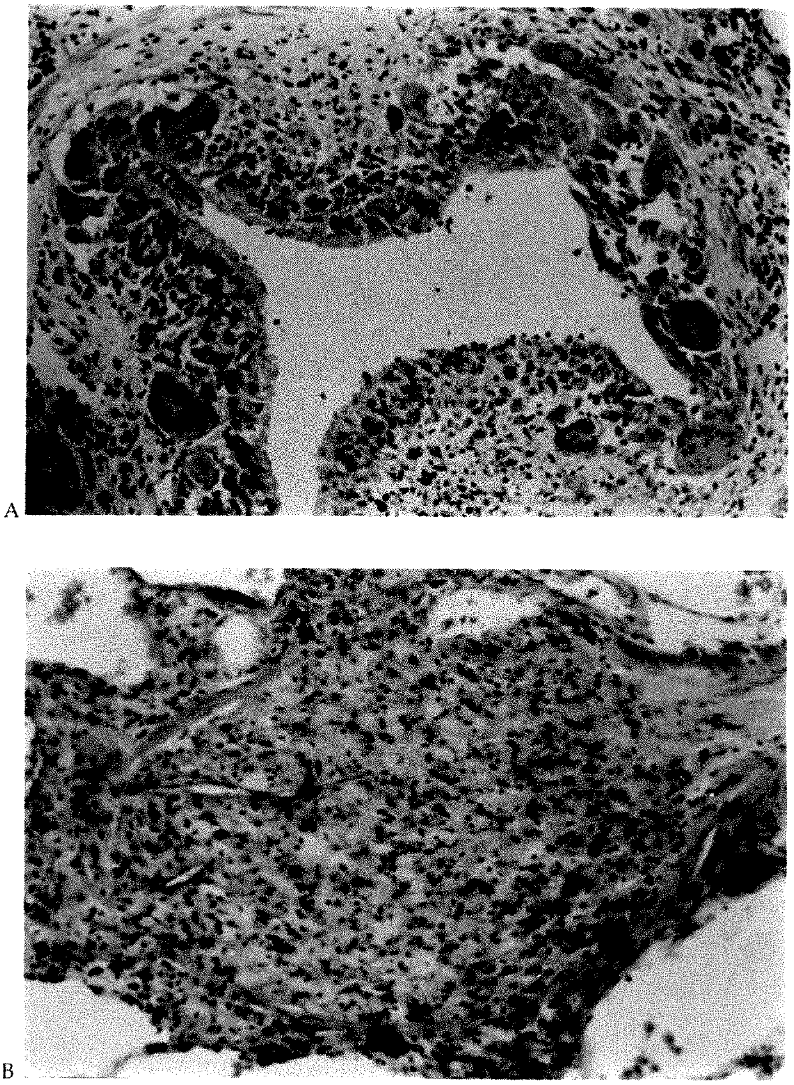

Fig 5. Obliterative bronchiolitis. (A) Cross-section (magnification, ×60 before 42% reduction) of a small bronchus infiltrated by various immunocompetent mononuclear cells. (B) End-stage of the disease: the lumen of the bronchus is obliterated by scar tissue.

Retransplantation of the heart and lungs then appears to be the only alternative.

Results After Heart-Lung Transplantation

Worldwide, 501 HLTxs have been performed since 1981 (as compared with 9,417 heart transplantations and 51 single and double lung replacements reported to the International Society for Heart Transplantation in the same period); approximately 40% of the interventions were performed during the last year. With increasing experience, the 30-day mortality decreased to less than 20%; 66.5% of the patients who were operated on worldwide between 1986 and 1988 are alive and well after 1 year.

The results of some individual groups are even better. The 1-year and 2-year survival rates of Stanford's most recent group [69] improved to 84.6% each (previous figures were 60% and 50%). For the same postoperative time, the group of researchers at Papworth hospital in Cambridge [70] reported survival in 78% and 68% of their patients.

First experiences are gained with cystic fibrosis and emphysema patients. Of 189 HLTx patients from Yacoub's group in London [12], 44 had cystic fibrosis. One patient also had liver failure and required combined heart-lung and liver replacement. Four of the patients died at an early stage, and 2 died at a late stage; the 1-year survival rate thus was 78%. The same group [71] reported a 1-year survival rate of 91% (10 of 11 patients) for patients with emphysema.

In 1989, in the hands of a few experienced groups, HLTx appears to be a clinical method with acceptable results. The donor shortage remains a major problem.

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CORRESPONDENCE

Sequel of the Internal Mammary Artery as a Systemic-to-Pulmonary Artery Shunt

To the Editor:

The recent paper by Longaker and associates [1] nicely illustrates the use of internal mammary artery for a right systemic–pulmonary anastomosis and, like previous reports [2, 3], enumerates many potential advantages of this technique. The first patient in whom my colleagues and I used this procedure, for tetralogy of Fallot with hypoplastic pulmonary arteries and major aortopulmonary collateral vessels, recently came to complete correction at 8 years of age. During the 4 years after his shunt, the patient had excellent palliation and the pulmonary arteries developed satisfactorily (Fig 1). His right arm pulses were normal, and there was a notable lack of hemorrhage from chest wall collaterals at sternotomy. However, the internal mammary artery proved to be extraordinarily friable, and gentle dissection of the shunt before commencement of cardiopulmonary bypass produced a large split in its wall. Even after institution of bypass, torrential hemorrhage precluded dissection of the artery, which was thus digitally occluded to maintain perfusion pressure during cooling. It was controlled finally during a period of low flow by oversewing the divided vessel with 6-0 monofilament suture supported with pericardial pledgets, packing the bed of the shunt with oxidized methylcellulose, and drawing the surrounding soft tissues together with large bites of 4-0 suture. The remainder of the operation was uneventful, and the patient was discharged home eight days later.

Despite its superficial resemblance to a classical Blalock-Taussig shunt, the internal mammary artery is a much more delicate structure, which probably should be managed like a Potts anastomosis at the time of closure. Although this shunt was easily accessable via a midline sternotomy, each time it was encircled with a ligature, the vessel disintegrated more proximally. It is possible that this resulted from a structural abnormality in the artery that caused it to become enlarged and thus attractive to use as a shunt in the first instance. Certainly, this experience has diminished our enthusiasm for the internal mammary artery-to-pulmonary artery anastomosis. We now reserve this procedure for patients with not more than modest enlargement of the internal mammary artery and very hypoplastic pulmonary arteries, to which other shunts would be unlikely to remain patent.

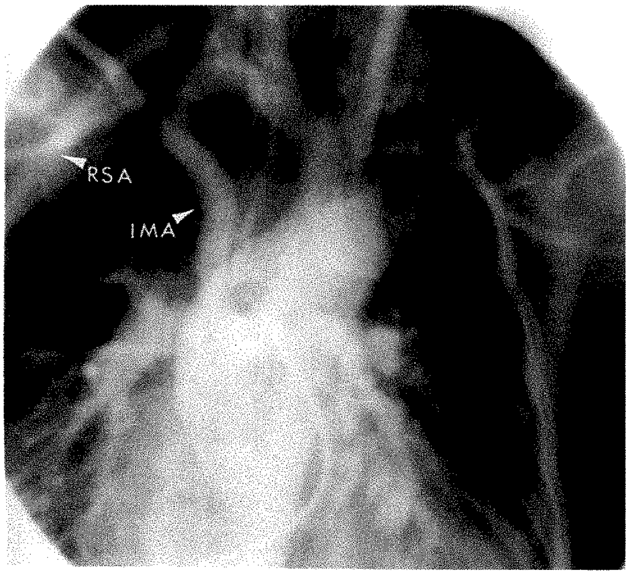

Fig 1. Ascending aortogram in the anteroposterior view 3½ years after internal mammary artery-to-right pulmonary artery anastomosis. (IMA = *internal mammary artery;* RSA = *right subclavian artery.)*

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Pericardial Flap

To the Editor:

Starr and Moore [1] and Todd and associates [2] describe the suture of the pericardium to the chest wall to prevent displacement of internal mammary artery grafts by the left upper lobe. When the internal mammary artery is dissected free of the chest wall and at least as proximal as the subclavian vein, as described by Green [3] and Flege [4], it lies along the mediastinum close to the phrenic nerve and cannot be displaced by the left upper lobe, obviating the need for the pericardial maneuvers.

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Reply

To the Editor:

Dr Flege raises a valid point that was not fully addressed in our article. Undoubtedly adequate proximal mobilization of the left internal mammary artery is an important step in reducing the incidence of undue tension on the left internal mammary artery by the anteromedial edge of the left upper lobe.

However, in certain patients, our experience is that this problem can still occur despite the adequate proximal dissection of the left internal mammary artery. These patients are often female, with chronically stiff, hyperinflated lungs that often meet in the

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midline anteriorly. The superior part of the lung edge seems "hard" and well defined. Whether these features are due to chronic lung disease or merely anatomical variation is difficult to assess.

Our suggestion was not intended to replace adequate proximal dissection, or the "pericardial incision" technique described by Dr Flege, but merely to supplement those in the occasional patient whose left upper lobe expansion still threatens to place tension on the left internal mammary artery graft.

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One-Stage Operation for Chronic Empyema

To the Editor:

The excellent article [1] on the use of extraperiosteal fluid plombage thoracoplasty in the treatment of 11 patients with chronic empyema thoracis serves a valuable function in demonstrating the practical utilitarianism of this procedure in obliterating residual pleural spaces.

As is so often the case with "new procedures," this operation to which Nakaoka and associates refer as "our new method" is really not new. The use of an "empty" plombage thoracoplasty, initially containing air and then displaced with transudated fluid such as blood and serum, has been widely used after pulmonary resections and to close other residual spaces. Max Chamberlain and associates [2] in 1953 referred to this as "extra periosteal plombage of the patient's subscapular collection of blood." James Pate and co-workers [3] described a similar procedure, called "air plombage," in 1958. Sixty-one patients had this procedure after pulmonary resection and demonstrated the steady reexpansion of the lung and obliteration or marked decrease in the size of the residual extrapleural space. In 313 upper lobe resections, without air plombage added, the complication rate was 19%. However, in the 61 patients in whom air plombage was used, the complication rate was only 1.6%. This procedure has been widely used, at least in our part of the country, by many people for over 30 years for pleural spaces remaining after resections, decortications, or empyema.

Nevertheless, any claims to priority are relatively insignificant. This is an excellent procedure and Nakaoka and associates demonstrate a well thought-out quantitation of remaining pulmonary function (for the first time) and demonstrate its use in improving function. Most pulmonary surgeons can benefit by their excellent presentation.

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Aortic Homograft for Aortic Valve Endocarditis

To the Editor:

I read with interest the article by Zwischenberger and associates [1] regarding aortic valve endocarditis and annular abscesses. I applaud them for their use of aortic homographs and would like to augment the literature by briefly describing 2 more cases in which the aortic root abscess had eroded into the right atrium with a resultant fistula.

The first patient was a 29-year-old non-drug abusing man who was seen in November 1988 with *Staphylococcus epidermidis* endocarditis and severe aortic insufficiency. Valve replacement with a St. Jude prosthesis was urgently undertaken and the patient did well for approximately a week, when recurrent aortic insufficiency ensued with fistulization of a now-present root abscess to the right atrium. Aortic valve replacement, debridement of the fistula tract and vegetation in the right atrium, and patching of the fistula with autologous pericardium was undertaken. The patient did well again for approximately a week, when recurrent aortic insufficiency without fistula was noted. On the third operation an aortic root replacement was done using a homograft with appropriate tailoring of the homograft to fill the abscess cavity. The homograft was anchored to the base of the abscess in the left ventricular muscle. Coronary reimplantation was accomplished, and postoperatively the patient has done very well without evidence of recurrent infection in short-term follow-up.

The second patient was a 52-year-old non-drug abusing man who was referred from another institution where a porcine valve had been placed for endocarditis after the organism could not be cultured. Aortic insufficiency had developed within two days after operation with resultant severe circulatory compromise and renal failure with a creatinine level of 5 mg/dL. Surgical findings consisted of a large root abscess with fistulization to the right atrium and vegetation formation in the right atrium. The fistula tract was debrided and repaired with autologous pericardium through the right atrium and a homograft was tailored to be seated into the left ventricular myocardium with coronary reimplantation. Renal function improved postoperatively, and in short-term follow-up the patient does not have any signs of recurrent infection.

I agree that the versatility of the aortic homograft is a great benefit when dealing with these difficult problems of infection.

Michael K. Wood, MD

Peninsula Hospital
Burlingame, CA 94010

Reference

1. Zwischenberger J, Shalaby T, Conti V. Viable cryopreserved aortic homograft for aortic valve endocarditis and annular abscesses. Ann Thorac Surg 1989;48:365–70.

Alternate Technique for Biopsy in Lung Transplantation Patients

To the Editor:

Lung transplantation is being done with increasing frequency. Its success has been improved by better patient selection criteria, the use of cyclosporine, and the current approach to bronchial anastomosis with the use of omentum. Transbronchial biopsies of the lung have been recommended and done as a method of evaluation of progress and recognition of problems such as rejection in transplant recipients. This communication details an alternate approach for pulmonary biopsies, which can be done repeatedly as needed.

An incision is made in the skin over the area of the fifth and sixth ribs in the mid or posterior axillary line. Two- to three-inch (5 to 8 cm) segments of ribs 5 and 6 are removed subperiosteally. The medial surface of the periosteum is left intact. The intercostal vessels are ligated at each extremity and the intervening portion is excised. With attention to detail, bleeding and pneumothorax are easily avoided. A sterile sponge is placed in the wound and the skin is closed. With this method obliterating pleural adhesions result, usually within 1 week, at which time the sponge can be removed and the skin again reapproximated. To hasten the process of pleural symphysis the sterile sponge can be wet with 50% glucose solution. The foregoing is a variation of the Monaldi procedure, which was used as an approach to drainage of giant apical tuberculous cavities [1].

The first stage of this procedure can be done at the time of the initial transplantation or at a time of election. If done at a later date a posterior incision may be preferred. At approximately ten days after the initial procedure one may introduce a needle with the patient under local anesthesia and take appropriate pulmonary biopsy specimens without fear of producing a pneumothorax. Biopsy specimens can be taken repeatedly as needed.

Inasmuch as bronchial anatomy is basically not an issue for the information needed in lung transplantation, the discomfort associated with bronchoscopy is avoided. The equipment for needle biopsy is readily available and less expensive.

Irving M. Madoff, MD

Departments of Cardiothoracic Surgery
St. Elizabeth's Hospital and The University Hospital
Boston, Massachusetts

Reference

1. Monaldi V. Tentativi di aspirazione endocavitaria nelle tuberculosi del polomone. Lotta Contro Tuberc 1938;9(9).

1989 Meeting Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association was held at the Phoenician Resort, Scottsdale, AZ, November 9–11, 1989. The President was Richard E. Clark, MD. Officers elected for the coming year are: *President*, Harvey W. Bender, Jr, MD; *President/Elect*, Robert M. Sade, MD; *Vice President*, Frederick L. Grover, MD; *Secretary-Treasurer*, Gordon F. Murray, MD, and *Secretary-Treasurer/Elect*, Hendrick B. Barner, MD.

The following 21 applicants were elected to membership:

Roy G. Bowling, MD
Louisville, KY

Duke E. Cameron, MD
Baltimore, MD

Paul L. Cammack, MD
Montgomery, AL

Robert G. Carlson, MD
Temple, TX

Eric L. Ceithaml, MD
Jacksonville, FL

Vincent R. Conti, MD
Galveston, TX

John R. Garrett, MD
Arlington, VA

Ronald C. Hill, MD
Morgantown, WV

Laurence F. Hiller, MD
Shreveport, LA

Eddie L. Hoover, MD
Nashville, TN

Richard A. Hopkins, MD
Washington, DC

Lance E. Landvater, MD
Raleigh, NC

C. Gregory Lockhart, MD
Richmond, VA

Michael L. Maggart, MD
Knoxville, TN

Barry D. Newsom, MD
Tuscaloosa, AL

Harvey I. Pass, MD
Bethesda, MD

Mark E. Sand, MD
Keesler Air Force Base, MS

Nicholas J. Sears, MD
Tampa, FL

George D. Vaughan III, MD
Winchester, VA

CDR Edward L. Woods
Bethesda, MD

William D. Spotnitz, MD
Charlottesville, VA

Elevated to senior membership were: Gilbert S. Campbell, MD, John P. Collins, MD, W. Clayton Davis, MD, Joseph W. Gilbert, Jr, MD, Charles A. Johnson, MD, Richard R. Lower, MD, W. Bensen McCutcheon, Jr, MD, Robert Trumbo, MD, and Watts R. Webb, MD.

The President's Award for the best scientific paper given at the 1988 meeting was presented to Robert A. Gustafson, MD, Gordon F. Murray, MD, Herbert E. Warden, MD, Ronald C. Hill, MD, and G. Edward Rozar, Jr, MD, for their paper "Stage I Palliation of Hypoplastic Left Heart Syndrome: The Importance of Neoaorta Construction."

The 1990 meeting will be held at the Hyatt Regency Cerromar Beach, Puerto Rico, November 8–10, 1990. Chairman of the Program Committee will be Donald C. Watson, Jr, MD, Chairman of the Postgraduate Committee will be D. Glenn Pennington, MD, and Chairman of the Membership Committee will be Lenox Baker, Jr, MD.

Gordon F. Murray, MD
Secretary-Treasurer
Southern Thoracic Surgical Association
111 East Wacker Drive
Chicago, IL 60601

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and the Southern Thoracic Surgical Association*

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Loma Linda International Conference on Pediatric Heart Transplantation, Palm Desert, California—March 11–14, 1990

For information on this meeting, contact Leonard Bailey, MD, Loma Linda International Heart Institute, Loma Linda University Medical Center, Loma Linda, CA 92350; or telephone (800) INTL-HEART.

Tenth Annual San Diego Cardiothoracic Surgery Symposium, San Diego, California—March 15–18, 1990

This symposium, entitled "Pathophysiology & Techniques of Cardiopulmonary Bypass: X," is sponsored by the Cardiothoracic Research & Education Foundation. For information on this symposium, contact Cardiothoracic Research & Education Foundation, PO Box 33185, San Diego, CA 92103; or telephone UnConventional, Inc, at (619) 692-9115.

Thirty-ninth Annual Meeting of the American College of Cardiology, New Orleans, Louisiana—March 18–22, 1990

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone 1 (800) 253-4636.

Annual Meeting of the International Society for Heart Transplantation, Fort Lauderdale, Florida—April 4–6, 1990

For information on this meeting, contact International Society for Heart Transplantation, 435 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-0828.

Modern Trends in Cardiac and Thoracic Surgery and Reunion of the Mark IV Club, Bristol, England—April 5–6, 1990

The symposium on modern trends in cardiac and thoracic surgery will be followed on April 7 by a reunion of the Mark IV Club (past residents of Ronald Belsey). For information on either of these meetings, contact Mrs Margaret Vickers, Symposium Coordinator, Department of Thoracic Surgery, Frenchay Hospital, Bristol BS16 1LE, England; or telephone 0272 701212, extension 2466.

General Thoracic Surgery, Las Vegas, Nevada—April 19–20, 1990

This meeting is sponsored by the American College of Chest Physicians and the University of Nevada School of Medicine. It is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information on this postgraduate course, contact ACCP, Division of Education, 911 Busse Highway, Park Ridge, IL 60068; or telephone (708) 698-2200.

Thirty-sixth Annual Meeting of the American Society for Artificial Internal Organs, Washington, DC—April 24–27, 1990

For information on this meeting, contact ASAIO Registration, PO Box C, Boca Raton, FL 33429.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660.

Seventieth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada—May 7–9, 1990

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Pulsed Lasers in Angioplasty, Tübingen, Federal Republic of Germany—May 11–12, 1990

This workshop is sponsored by the European Society of Cardiology, the Working Group of Coronary Flow and Angina Pectoris, and the European Association of Radiology. For information on this meeting, contact K. R. Karsch, Department of Cardiology, Medical Clinic, University of Tübingen, Otfried-Müller-Str 10, D-7400 Tübingen, Federal Republic of Germany.

Third International Symposium on Echocardiography and Doppler in Cardiac Surgery, Vienna, Austria—May 9–12, 1990

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450 Vienna, Austria; or telephone +43/1/23 69/2642 (telex: 11 18 03; facsimile: +43/1/23 69/648).

Eleventh Annual Scientific Session of the North American Society of Pacing and Electrophysiology, San Diego, California—May 31–June 2, 1990

For information on this meeting, contact the North American Society of Pacing and Electrophysiology, 13 Eaton Court, Wellesley Hills, MA 02181; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

Eighth Annual Uniformed Services University of Health Sciences Cardiothoracic Surgery Symposium, Washington, DC—May 31–June 2, 1990

For information on this meeting, contact Fred H. Edwards, MD, Department of Thoracic Surgery, Walter Reed Army Medical Center, Washington, DC 20307-5001; or telephone (202) 576-1433.

The Society for Vascular Surgery/International Society for Cardiovascular Surgery, Los Angeles, California—June 4–6, 1990

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Seventh International Congress Cardiostim 90, Nice, France—June 20–23, 1990

Cardiostim gathers several scientific events: Cardiostimulation 90 (cardiac pacing, electrophysiology, defibrillation), International Conference on High-Resolution ECG and Late Potentials, Fifth World Congress on Catheter Ablation, Cardio-Pharmaco 90, and Cardio-Rythmo 90. For information on this meeting, contact Secretariat Cardiostim 90, Department of Cardiac Pacing, Centre Chirurgical Val D'Or, 16, rue Pasteur, 92211 St. Cloud Cedex, France; or telephone (1) 46.02.70.72 (facsimile: (1) 46.02.05.09).

Sixteenth Annual Meeting of The Western Thoracic Surgical Association, Coronado, California—June 20–24, 1990

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Internal Thoracic Artery for Myocardial Revascularization, Toulouse, France—June 27–29, 1990

For information on this meeting, contact the Secretary of the Symposium, Department of Cardiovascular Surgery, Rangueil University Hospital, 31054 Toulouse Cedex, France; or telephone 61.32.26.51 or 61.32.26.53 (telex: 530 826 F).

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

Thirty-ninth Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary—September 9–12, 1990

For information on this meeting, contact Budapest Convention Centre, H-1444, PO Box 233, Budapest XI, Jagello u 1-3, Hungary; or telephone (361) 852-507 (facsimile: (361) 665-636; telex: 22-7717).

Fourth Annual Meeting of the European Association for Cardio-thoracic Surgery, Naples, Italy—September 17–19, 1990

For information on this meeting, contact the Organizing Secretariat, MCM, Rione Sirignano, 5, 80121 Naples, Italy; or telephone (0)81/7611085-7611277 (facsimile: (0)81/664372; telex: 710626).

Interim Meeting of The Society of Thoracic Surgeons, Chicago, Illinois—September 22–23, 1990

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 440 Park Avenue South, New York, NY 10016 (telephone: (212) 684-5540; facsimile: (212) 545-0651). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $15.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3695). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

Please respond to Box 102. 102G/C

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

Please respond to Box 105. 105C/B

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

Please respond to Box 144. 144E/D

Cardiothoracic surgeon wanted for a busy, expanding, 3-man, private practice group in the Midwest. Applicant must be ABTS eligible or certified. Prefer recent graduate with some background in electrophysiologic surgery. Please send curriculum vitae.

Please respond to Box 189. 189H/G

Cardiovascular and thoracic surgeon wanted to join busy practice in Fort Lauderdale, Florida. Recent US medical graduate preferred.

Please send CV to I. Tabry, MD, 2773 NE 37th Drive, Fort Lauderdale, FL 33308. (Telephone: (305) 561-9781 after 9:00 PM.) 208J/C

Cardiac-thoracic surgeon, needed for expanding program on west coast of Florida. Excellent opportunity, private practice, primarily adult cardiac including cardiac transplantation. BC/BE required. Please send CV.

Please respond to Box 226. 226K/D

Cardiothoracic surgeon, BE/BC, wanted to join surgeon in active cardiac/thoracic/vascular surgical practice in northern Alabama community of 80,000 (300,000 population draw). Clinical practice in two community hospitals. Lake/mountain recreation facilities. Generous compensation, future partnership.

Please write Sara Fleming, Business Manager, 801 Gaines Ave, Suite 305, Gadsden, AL 35903; (205) 492-9360. 237L/E

Cardiothoracic surgeon wanted to join established practice in Long Island, NY, area. Recent graduate preferred. Please submit curriculum vitae and references.

Please respond to Box 238. 238L/B

Associate Director for Heart Transplantation is urgently needed for rapidly expanding heart transplantation program in California.

Please respond with curriculum vitae to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 240L/K

Assistant surgeon—experienced in cardiothoracic surgery to first assist in the operating room. Active adult and pediatric cardiovascular surgery practice in southern California.

Please respond with curriculum vitae and outline of surgical experience to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 241L/K

Cardiothoracic and vascular surgeon, BC/BE, recent graduate to join private practice of adult cardiac, pulmonary, and vascular surgery located in New Jersey. Please submit curriculum vitae.

Please respond to Box 243. 243L/C

Cardiac surgeon, board certified or eligible, needed for a growing cardiac surgery program in the Southeast. Excellent opportunity for someone primarily interested in adult cardiac surgery.

Please respond to Box 248. 248L/B

Thoracic surgeon. A 230-physician multispecialty prepaid group in Hawaii is seeking a qualified MD to accept the second thoracic surgery position. Must be experienced in adult cardiac, general thoracic, and peripheral vascular surgery. Excellent fringe benefits. Malpractice paid.

Please direct curiculum vitae to Hawaii Permanente Medical Group, Inc, 3288 Moanalua Rd, Honolulu, HI 96819. An equal opportunity employer. 250L/B

Cardiovascular and thoracic surgeon, board eligible/certified, wanted to join well-established private practice located in Ft. Lauderdale, FL. Send CV.

Please respond to Box 251. 251L/E

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to Box 252. 252L/F

Thoracic-vascular surgeon wanted to join busy practice in Northeast. Board certified or eligible. Interested in practice of vascular and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 254. 254L/F

Cardiothoracic and vascular surgeon wanted to be first assistant. Twenty years experience preferred. Interested in practice of cardiac, vascular, and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 255. 255L/F

Cardiothoracic surgeon—to join a 2-man private practice in cardiac, thoracic, and vascular surgery in the Great Lakes region. Must be board certified or eligible. Recent graduates considered. Send curriculum vitae.

Please respond to Box 260. 260L/E

Cardiothoracic surgeon, experienced in cardiac arrhythmia surgery, to join well-established cardiac surgical group in central Florida. Send CV.

Please respond to Box 267. 267A/C

Cardiovascular and thoracic surgeon, BE/BC, to join established private practice in San Francisco Bay area. Practice includes adult cardiac, thoracic, and vascular surgery. Initial contact should include curriculum vitae and references.

Please respond to Box 268. 268A/C

Cardiothoracic surgeon: Private practice position, Great Lakes, adult cardiothoracic and vascular surgery. Must be currently active in cardiac surgery. Send CV and references.

Please respond to Box 269. 269A/C

Cardiothoracic surgeon: The Oregon Health Sciences University, Division of Cardiopulmonary Surgery, with strong active programs in all aspects of cardiopulmonary surgery and heart transplantation, has an academic position available at the Assistant Professor level. Candidates should be eligible for or certified by the American Board of Thoracic Surgery. Outstanding opportunity for an individual with excellent clinical skills, a track record of academic productivity, and a commitment to research and teaching. Two to 4 years of postresidency clinical experience is highly desirable.

Applicants are invited to respond with curriculum vitae to Adnan Cobanoglu, MD, Professor and Chief, Division of Cardiopulmonary Surgery, The Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201. 270AB

Chairperson, Department of Thoracic-Cardiovascular Surgery. Winthrop-University Hospital, a 533-bed tertiary care hospital of SUNY Stony Brook, is seeking candidates to chair its cardiothoracic department. Applicants should have strong clinical, teaching, and administrative skills, as well as a commitment to research. The department conducts a fully approved open heart program and performs a large volume of thoracic and vascular surgery. The hospital will support a fellowship program and research activities.

Send CV to Alan Fein, MD, Chairman, TCV Search Committee, Winthrop-University Hospital, c/o 222 Station Plaza No., Suite 400, Mineola, NY 11501. 273A/C

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland OR 97213-2282. 274A/F

Cardiovascular and thoracic surgeon: Position available for a board certified or board eligible to join practice in Northeast involved in adult cardiac, thoracic, and vascular surgery. Association will lead to partnership. Excellent fringe benefits. Please send curriculum vitae.

Please respond to Box 275. 275A/F

Cardiothoracic transplant surgeon, board certified or eligible, wanted to join established practice. Experience required in transplantation, adult cardiac surgery, and thoracic surgery. Northwest city with easy lifestyle and outdoor activities. Salary leading to partnership.

Please respond to Box 276. 276A/C

Cardiac surgeon, board eligible/certified, with at least 2 years experience in adult cardiac surgery, wanted to join well-established 2-surgeon practice located in south Florida.

Please respond to Box 277. 277A/C

Cardiac surgeon sought for beautiful Rocky Mountain region. 200 cases per year in a 282-bed regional hospital. Excellent salary and benefits with bonus incentives leading to partnership after third year. Outdoor activities abound in excellent living environment. BC/BE required. Please respond with curriculum vitae and references.

Please respond to Box 280. 280BC

Cardiovascular and thoracic surgeon, board-eligible/certified, wanted to join cardiothoracic surgical group in Philadelphia area at university-affiliated large teaching hospital. Please respond wih curriculum vitae and references.

Please respond to Box 282B. 282B

Cardiovascular surgeon, board certified or eligible, US graduate; immediate opening to join a 2-man group in large Midwestern city. Respond with curriculum vitae and references.

Please respond to Box 283. 283B

Thoracic surgeon: Excellent opportunity for experienced thoracic surgeon to join well-established hospital-based practice in general thoracic and vascular surgery. Hospital located in attractive New England coastal community and is affiliated with prestigious teaching institutions and medical schools.

Please contact Jeanne Dowrick, Fulton, Longshore & Assocs, 527 Plymouth Rd, Plymouth Meeting, PA 19462; telephone (800) 346-8397 or (215) 834-6780. 284B/D

Mobile, Alabama: cardiothoracic surgeons—The University of South Alabama College of Medicine will have two faculty positions available in July 1990. Candidates must be board eligible or board certified. Experience in both congenital and adult cardiothoracic diseases preferred.

Please forward curriculum vitae to J. Raymond Fletcher, MD, PhD, Professor and Chairman, Department of Surgery, University of South Alabama, College of Medicine, 2451 Fillingim St, 721 Mastin Building, Mobile, AL 36617. The University of South Alabama is an affirmative action/equal opportunity education institution. 286B

Noncardiac thoracic and vascular surgery opening . . . established 2-man general surgery practice located in north Georgia seeks third BE/BC associate. Practice to include general surgery, noncardiac chest and peripheral vascular surgery.

Contact Aaron Risen, Suite 260, Browenton Place, 2000 Warrington Way, Louisville, KY 40222; 1-800-626-1857. 289B

Cardiothoracic and vascular surgeon, BC/BE, to join well-established, nonrestricted private practice affiliated with tertiary medical center in Akron, Ohio. 80%–90% of surgery performed is cardiac with interest in adult acquired heart disease. Opportunity to expand existing practice at medical center and develop thoracic surgery practice in two nearby community hospitals.

Contact Barbara Driscol, 3645 Warrensville Center Rd, Shaker Heights, OH 44122; (216) 991-9770. 290B

Cardiovascular and thoracic surgeon: Position available for board certified or board eligible person to join busy practice involved in adult cardiac, thoracic, and vascular surgery in major New England city. Association will lead to partnership. Excellent fringe benefits. Please send curriculum vitae.

Please respond to Box 291. 291B

Cardiothoracic surgeon interested in joining an established practice in the Southwest. Must be experienced in adult cardiac, pulmonary, and vascular surgery. Must be board certified/board eligible. Please respond with curriculum vitae.

Please respond to Box 292. 292B

Cardiovascular and thoracic surgeon, BC/BE, recently trained to join an established 3-man private practice group in Southeastern coastal capital city and two-university town. Great hunting, fishing, and sports. Submit CV and references.

Please respond to Box 293. 293B/E

A busy cardiothoracic group in the NYC area is looking primarily for a thoracic surgeon with potential for cardiac surgery in the future. Excellent salary and benefits. Respond with curriculum vitae.

Please respond to Box 211. 211J/C

SITUATIONS WANTED

Cardiothoracic surgeon, 33, American, university trained, wishes to relocate. ABS, BE for ABTS. Experience in IMA and AICD surgery. Seeks position in private practice or academics. Curriculum vitae and references upon request.

Please respond to Box 262. 262L/B

Cardiovascular and thoracic surgeon, 45, ABS, ABTS, seeks relocation. Twelve years private practice and university experience.

Please respond to Box 271. 271A/C

42-year-old cardiac surgeon, American trained, ABS certified, ABTS eligible. Currently practicing in the Middle East. Has considerable experience in valve surgery. Wishes to relocate to the US but will require a visa. Would consider joining a group or research project.

Please respond to Box 285. 285B/D

Cardiovascular and thoracic surgeon, American, University trained, 36, wishes to relocate. ABS certified, ABTS eligible. Interested in joining a group or initiating a new program.

Please respond to Box 288. 288B/D

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 222K/D

Cardiopulmonary surgery fellow: Immediate opening of a clinical position for 1 year in a busy university service that performs adult cardiac surgery, thoracic surgery, pediatric heart surgery, and cardiac transplantation. The Fellow will be given responsibilities in perioperative care and as assistant and operating surgeon based on prior experience. Ideal position for a senior surgical resident who would like to attain additional experience in cardiopulmonary surgery or a resident waiting to enter a thoracic surgery residency.

Please respond with curriculum vitae to Adnan Cobanoglu, MD, The Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201. 242L/B

Fellowship in pediatric cardiovascular surgery available July 1990. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40's.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453; or telephone (312) 857-3029. 253L/D

Fellowship in adult cardiac surgery available for 1 or 2 years in private program performing over 600 open heart procedures yearly. General surgery training required. ECFMG and visa qualified foreign applicants accepted.

Send curriculum vitae to Donald R. Kahn, MD, 817 Princeton Ave, Suite 300, Birmingham, AL 35211. 263L/B

Lung transplantation fellowship. Available July 1, 1990. Active lung transplant program offers a surgeon the opportunity to spend 1 or 2 years in a rich pulmonary cellular immunology laboratory. Applicants may wish to apply for a Master's or PhD thesis in experimental surgery. In addition, the clinical responsibilities will include primary care for preoperative and postoperative management of transplanted patients. The Fellow will be involved in both donor procurement and recipient transplantations.

Submit complete curriculum vitae to Hani Shennib, MD, McGill Lung Transplant Program, The Montreal General Hospital, 1650 Cedar Ave, Suite 9827, Montreal, Que, Canada H3G IA4. 281B

Postresidency clinical fellowship available in cardiopulmonary surgery with group performing over 1,000 cardiac procedures per year. Up to 25% research opportunity option available. Complete training in cardiopulmonary surgery required. US graduates must be eligible for Oregon license. Foreign medical graduates must be eligible for J-l or H-l visa. Fellowship for 1 to 2 years beginning July 1990 or January 1991.

Please send CV to Albert Starr, MD, 9155 SW Barnes Rd #240, Portland, OR 97225. 287B/D

CARDIAC SURGERY FELLOWSHIPS & ASSOCIATE POSITIONS IN CARDIAC SURGERY

The Cleveland Clinic Foundation's Department of Cardiovascular Surgery performs 3000 open heart operations annually with an increasing proportion of either complex procedures or reoperation. Active sections exist in all facets of adult cardiac surgery including: reparative valvular procedures, electrophysiological surgery, cardiac transplantation, and circulatory support. Both clinical and experimental research opportunities exist.

FELLOWSHIP
A 1-2 year fellowship is available for individuals interested in board equivalent training in cardiac surgery. This program covers all aspects of adult cardiac surgery including intensive care unit experience.

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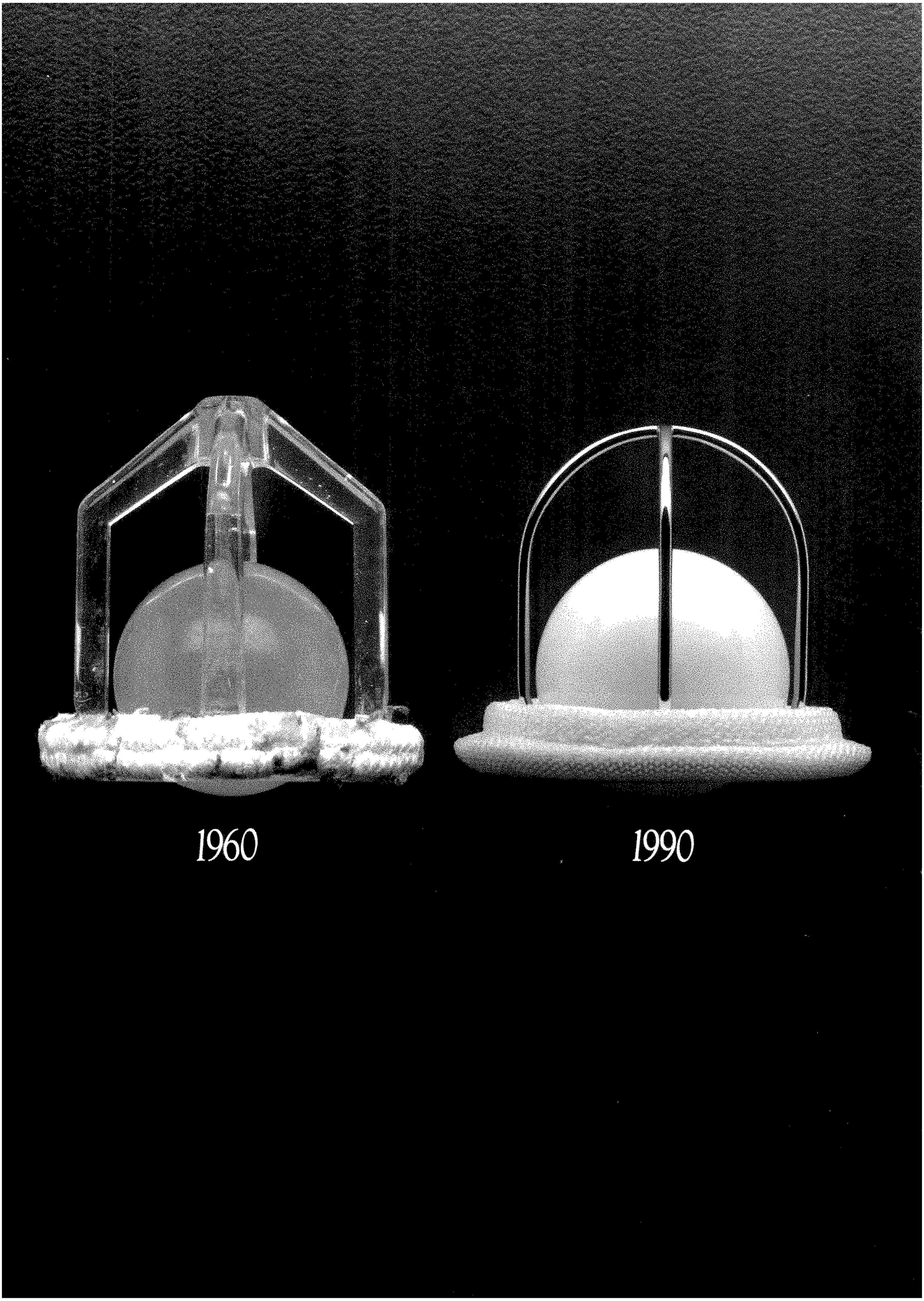

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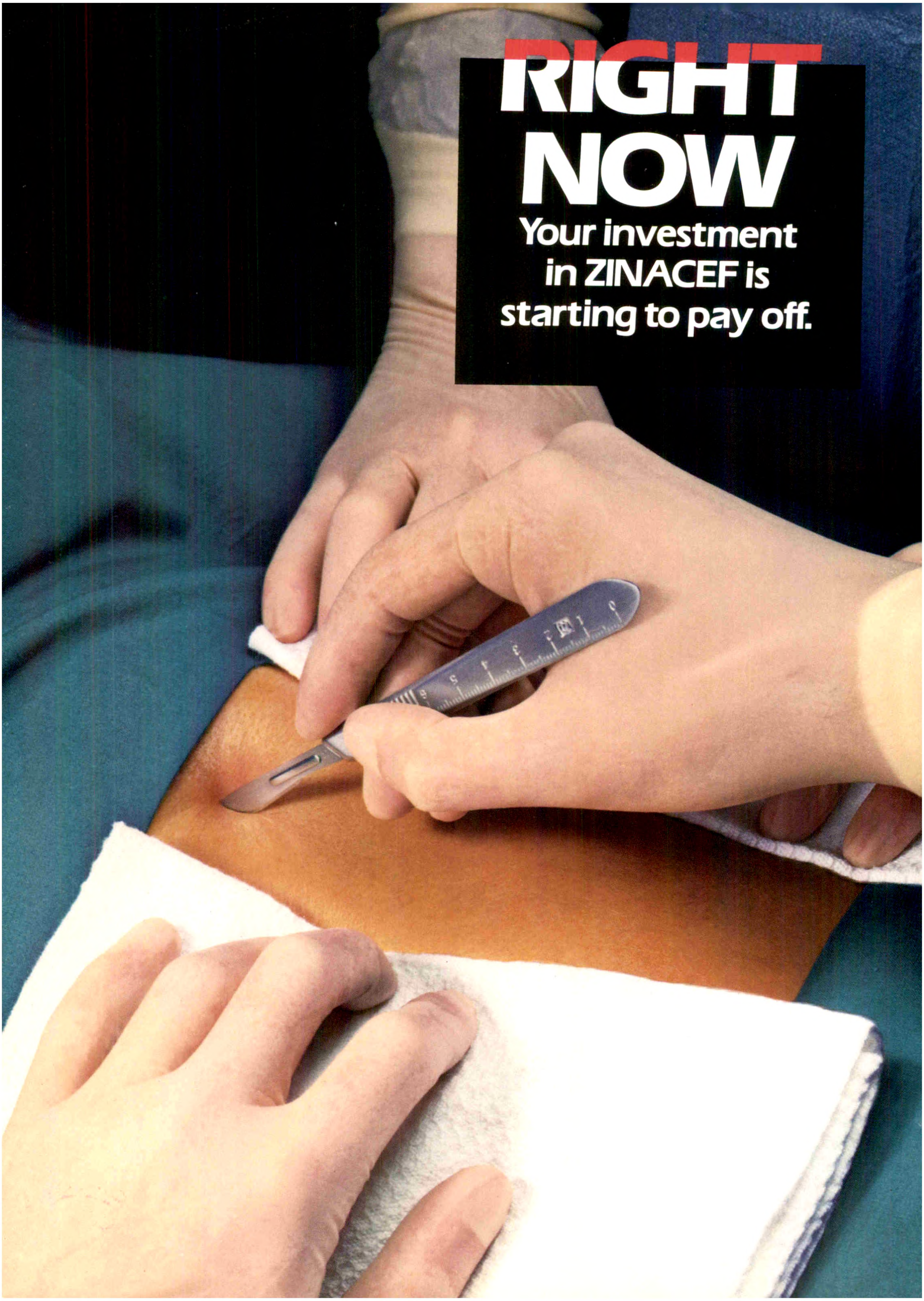
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1. Slama TG, Sklar SJ, Misinski J, et al: Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. *Antimicrob Agents Chemother* 1986;29:744-747.
2. Haley RW, White JW, Culver DH, et al: The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. *JAMA* 1987;257:1611-1614.

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INDICATIONS AND USAGE: ZINACEF® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

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2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* sp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* sp, and *Enterobacter* sp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* sp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *N meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *N gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. ZINACEF has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to ZINACEF.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, ZINACEF may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF® (sterile cefuroxime sodium, Glaxo) should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of ZINACEF has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that ZINACEF therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: ZINACEF® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although ZINACEF® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving ZINACEF.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since ZINACEF is excreted in human milk, caution should be exercised when ZINACEF is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: ZINACEF® is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence was seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

HOW SUPPLIED ZINACEF® is a dry, white to off-white powder supplied in vials and infusion packs.

Each vial contains cefuroxime sodium equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime. ZINACEF in the dry state should be stored between 15° to 30°C (59° to 86°F), and protected from light.

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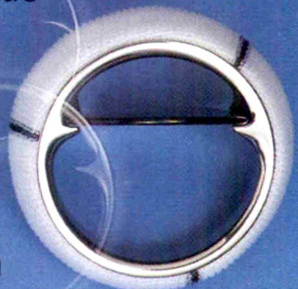

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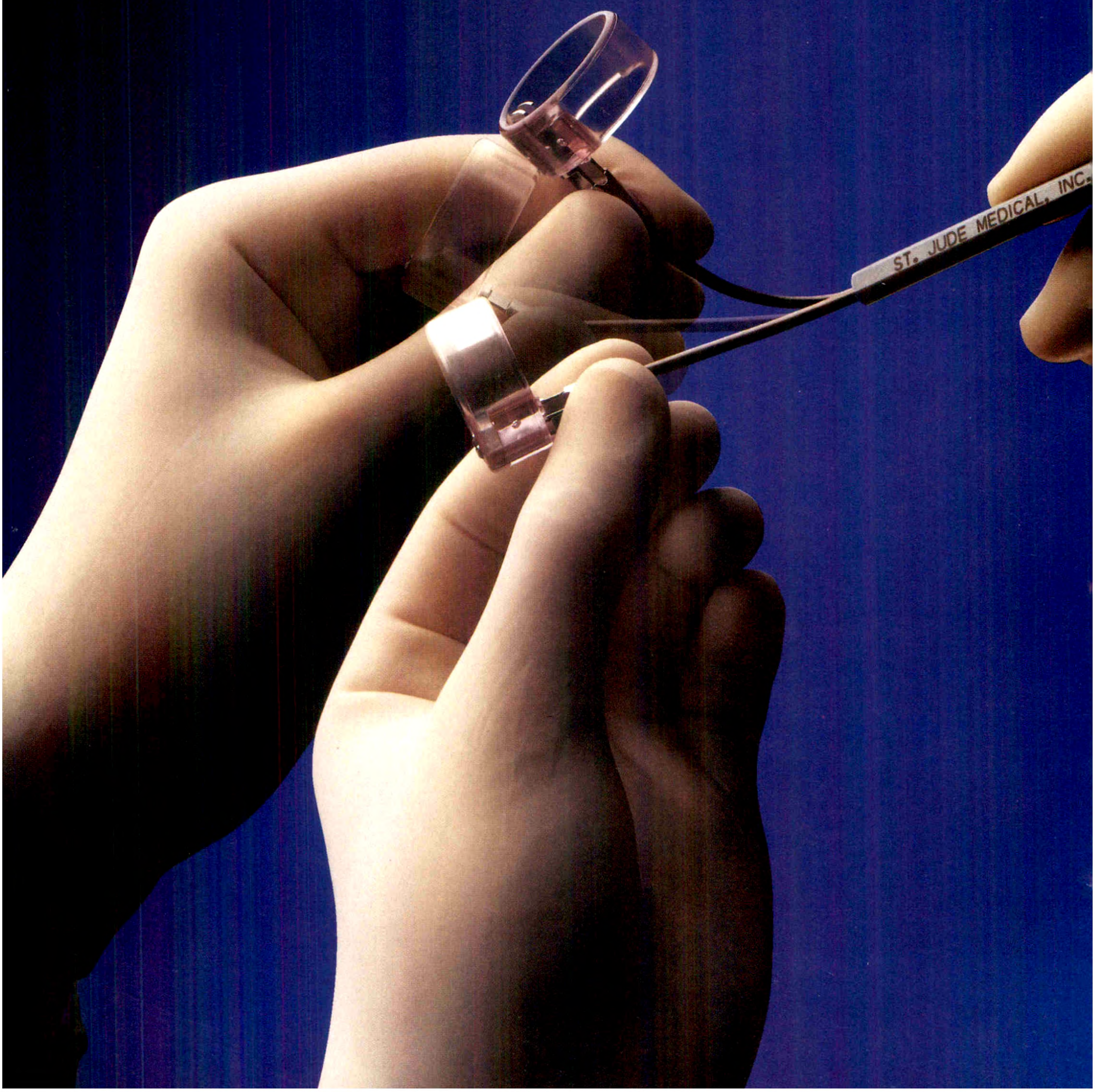

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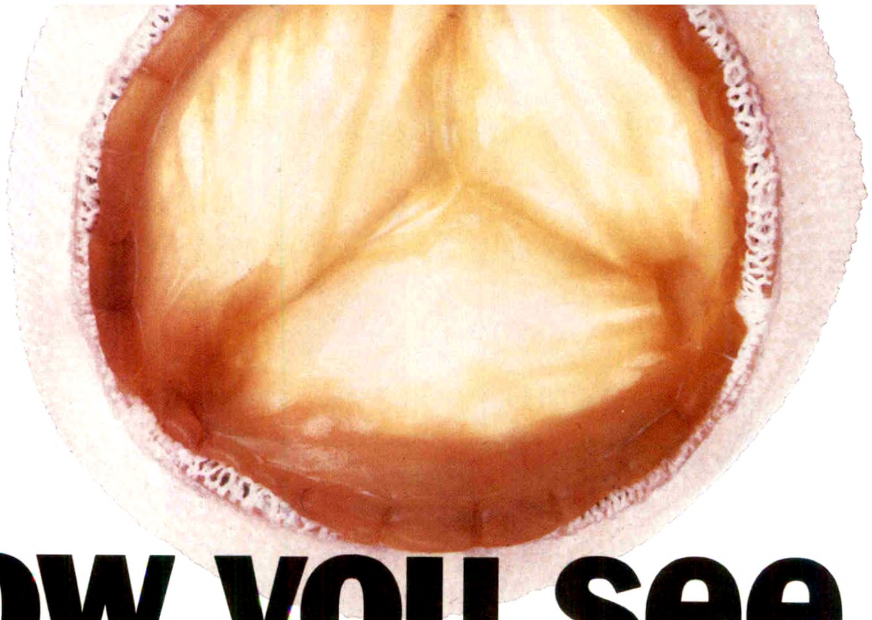

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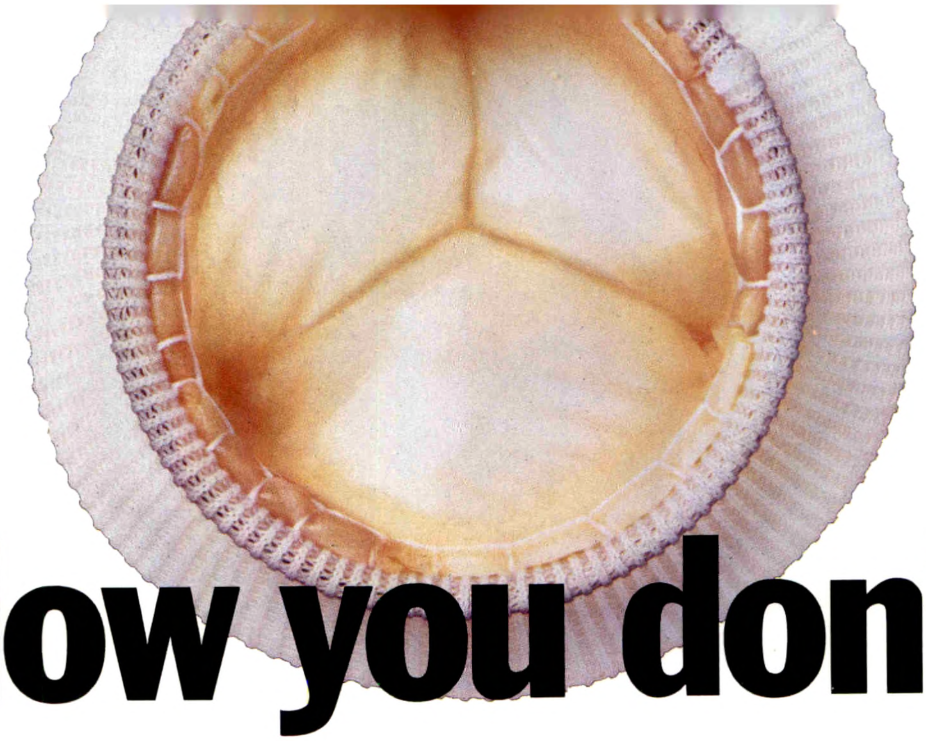

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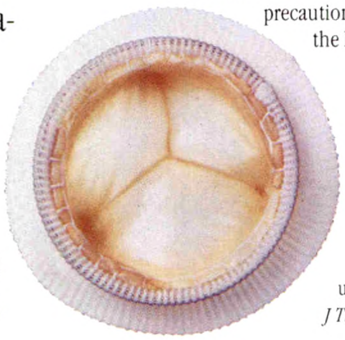

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1. DiSesa VJ, Allred EN, Kowalker W, et al: Performance of a fabricated trileaflet porcine bioprosthesis: Midterm follow-up of the Hancock modified-orifice valve. *J Thorac Cardiovasc Surg* 1987;94:220-224.

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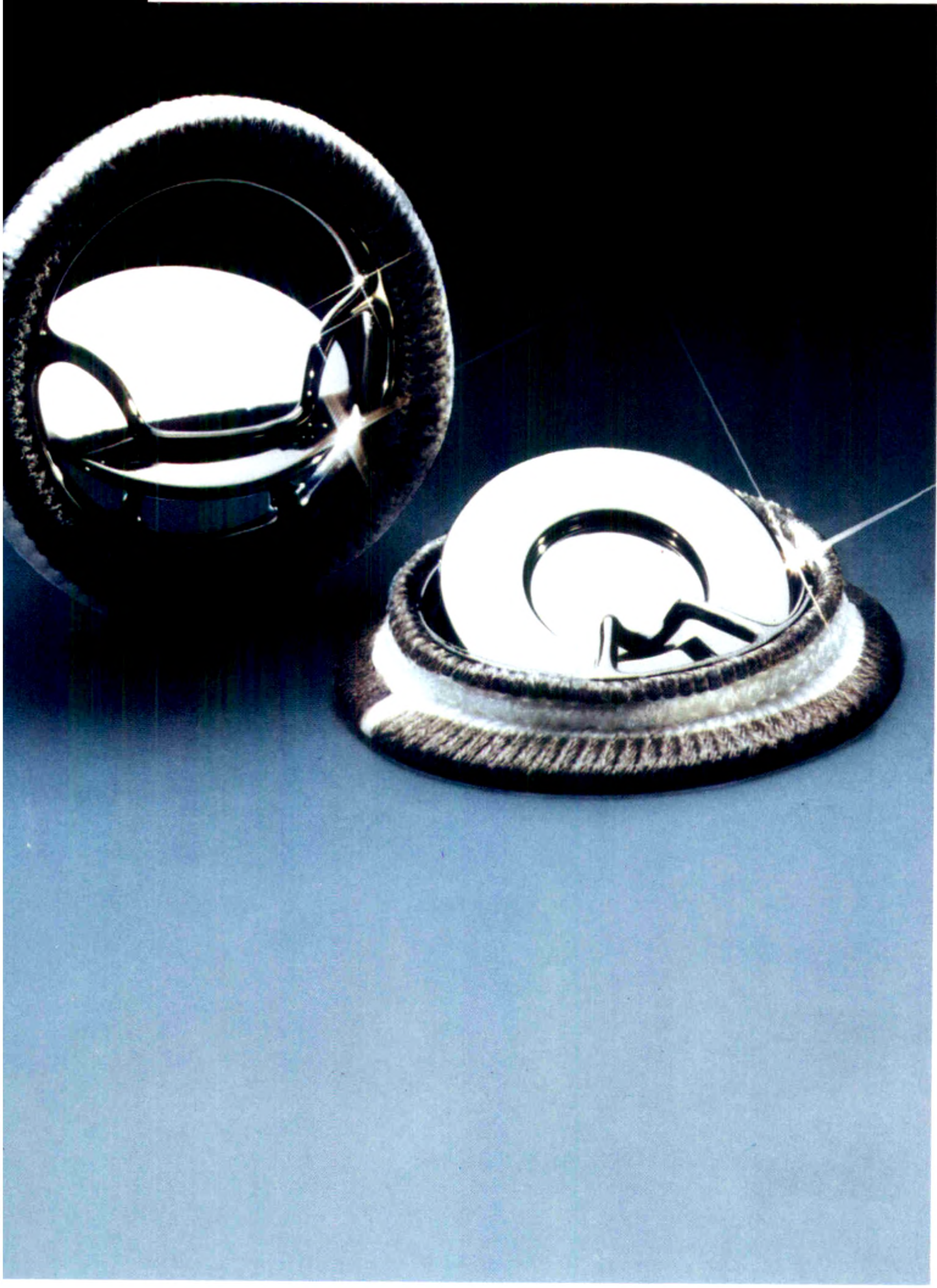

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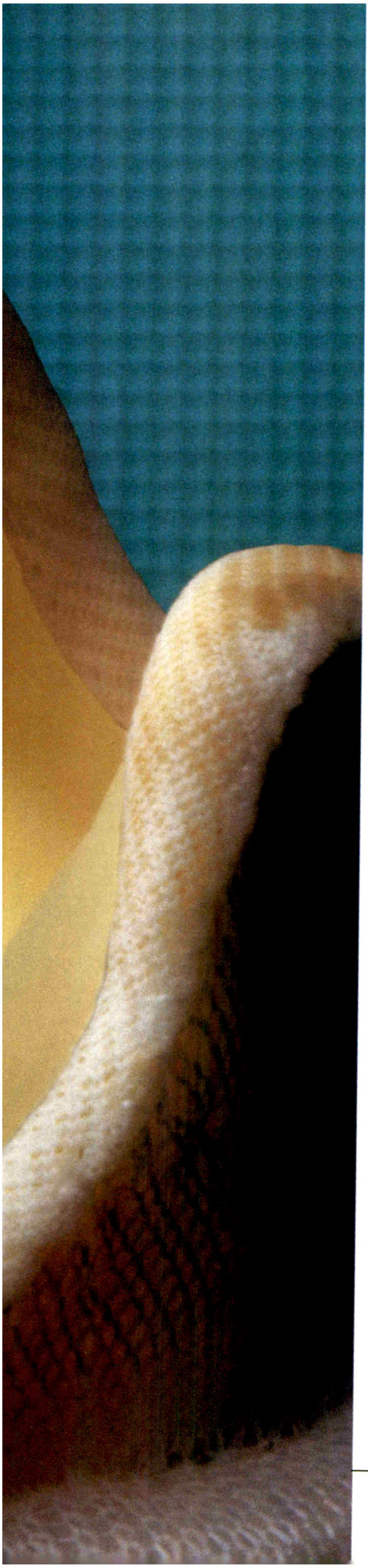

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Indications: Bioprostheses are indicated for use in patients suffering from valvular heart disease. Aortic and mitral valvular heart disease are conditions involving any of the following: obstructions of the heart valves, or stenosis; leakage of the valves, known as regurgitation or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions. Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia. Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy. The Carpentier-Edwards bioprosthesis is intended for use in patients whose aortic or mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic or mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis. **Warnings:** For Single Patient Use Only In the presence of conditions affecting calcium metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, in the presence of severe systemic hypertension, and in patients who are on maintenance hemodialysis. The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must **not** be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards bioprostheses to calcification as compared to other commercially available porcine valves. **Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician. Baxter International Inc. is the owner of the following US patent which covers the products described herein: 4,106,129. Patent numbers in foreign countries supplied upon request. See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information. Carpentier-Edwards® is a registered trademark of Baxter International Inc.

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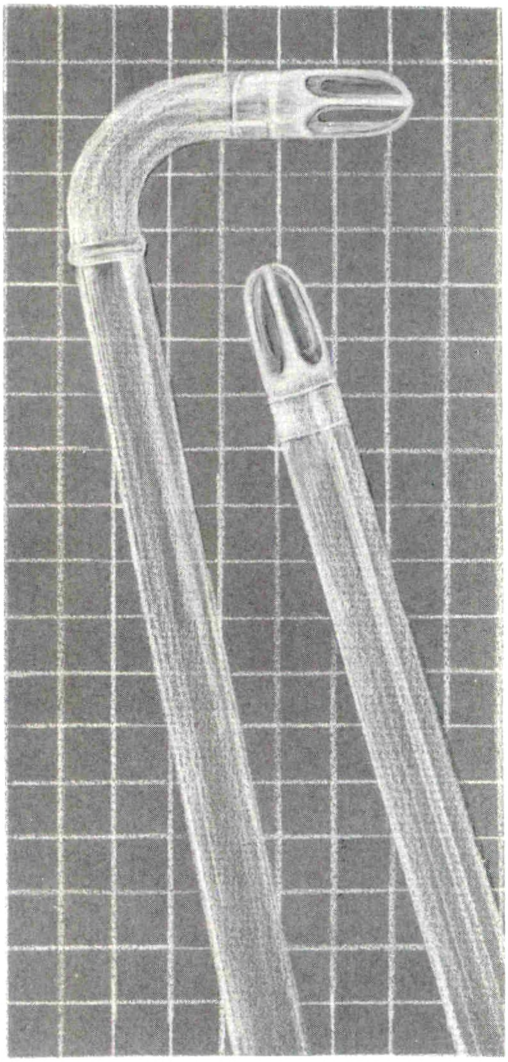

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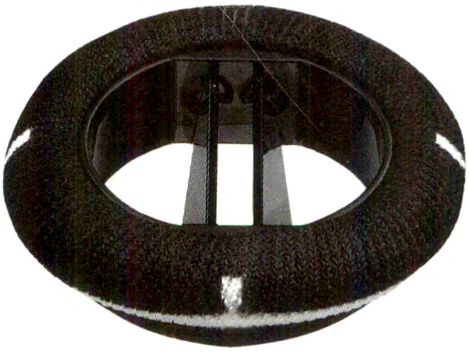

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Perioperative Multimodality Management of Esophageal Cancer: Therapeutic or Investigational?

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Until relatively recently, only resection or irradiation, alone or in combination, was used to treat cancer of the esophagus. Therapeutic results were almost invariably poor. This gave the impetus to explore alternative treatment methods for this disease [1, 2]. The failure in the treatment of this disease by resection alone can be attributed to two facts: (1) the location of the esophagus precludes application of the principle of wide resection, and (2) most patients with carcinoma of the esophagus already have contiguous spread and metastases when seen initially. Systemic disease requires systemic therapy. This is the reason for using chemotherapy. Because chemotherapy has a local cancerocidal effect and radiosensitizing properties, the hypothesis is that the combination of chemotherapy and irradiation improves local and systemic control of the disease.

In this issue of *The Annals*, Orringer and associates [3] report their initial experience in treating esophageal carcinoma with chemotherapy and radiotherapy followed by transhiatal resection of the esophagus. Their series includes almost equal numbers of adenocarcinomas and squamous cell carcinomas, and they indicate that adenocarcinoma and squamous cell carcinoma responded equally to multimodality therapy. At Wayne State University, we have treated a few patients with adenocarcinomas, but the response rate was somewhat lower than in squamous cell carcinoma. Orringer and associates used a triple-drug regimen consisting of cis-platinum. vinblastine, and 5-fluorouracil, combined with fractionated irradiation, before transhiatal resection of the esophagus. In an innovative technique, the 5-fluorouracil was given by a continuous infusion over 21 days. Transhiatal resection of the esophagus was accomplished after a suitable period required for recovery from myelosuppression caused by the chemotherapy.

See also page 348.

Orringer and associates report that most of the patients involved in the study suffered tolerable degrees of a variety of drug and radiation toxicities. However, 2 patients died from causes directly attributable to the chemotherapy. This may serve as a caveat that administration of chemotherapy has serious hazards even under close monitoring. Orringer and associates achieved an operability rate of 95%. At operation 2 patients had nonresectable disease, and in a third patient, microscopic disease was left behind. Another patient was found to have metastatic brain disease in the early postoperative period. These four occurrences point to the difficulty of preoperative staging of esophageal carcinoma.

There were neither postoperative complications in the form of delayed wound healing or anastomotic leaks nor any instances of respiratory insufficiency for which chemotherapy and irradiation could easily be blamed. Orringer and associates achieved an enviable mortality rate of 2%; their reported complete response rate of 27% is consistent with our earlier articles dealing with multimodality treatment of cancer of the esophagus [1, 4]. The median survival of the entire group is 29 months and the cumulative survival at 3 years is 46%. The 11 patients who had a complete response are still alive with a median follow-up of 36 months. These findings suggest beneficial effects from the multimodality therapy that was used.

At Wayne State University, the operative mortality rate was higher (14.5%). We and others have lost patients who had an uneventful esophagectomy because of the occurrence of respiratory insufficiency. This was attributed to the toxicity of a high inspired oxygen fraction administered during operation on lungs damaged by radiation and chemotherapeutic agents. We do not attribute our high complication and mortality rate to our lower rate of transhiatal esophagectomies. We usually attempt removal of the esophagus through the transhiatal route and anastomose the stomach to the esophagus in the neck. Our most common cause for abandoning transhiatal resection is dysrhythmia. We believe that our mortality and complication rates are due to our inner city population, which is inherently at a higher operative risk.

The immediate benefit of combined treatment is complete disappearance of the cancer in a substantial number of patients. The reduction of tumor size makes the resection easier and effects an increased resectability rate. Our experience with transhiatal esophageal resection began when we operated for the first time on a patient who had a complete response. The resection was done with facility, as if one were resecting a normal esophagus. However, the real question is whether or not complete response confers long-term survival benefit. From the report by Orringer and associates it seems so. Similar to results in our series, Orringer and associates reported 11 complete responders who are still alive with a median follow-up of 36 months. From our initial series, 6 patients (14.5%) survived for 5 years; 5 of these patients were complete responders. These 5 patients represent a 45% 5-year survival rate among our 11 complete responders. Encour-

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aging as our experience has been, we nonetheless must analyze the true significance of the findings.

In about 70% of our patients, carcinoma recurred in the form of distant metastases. This fact engendered controversy as to the need for operation in patients who had a complete response. Proponents for abandoning resection after a complete response argued that when esophageal carcinoma recurs it does so predominantly at a distance from the primary tumor. They argued that resection of the esophagus adds the risk of surgical mortality, and does not significantly influence survival [4]. The argument for resecting the esophagus is that a true response can be determined only after a thorough pathological examination of the resected esophagus. After chemotherapy and irradiation, the esophagus may contain microscopic residual disease that is undetectable by presently available methods. Therefore, patients who do not have resections may be denied their opportunity for cure.

Recently, 20 patients at Wayne State University were enrolled in a pilot study of nonoperative therapy for squamous cell carcinoma of the esophagus. 5-Fluorouracil, cisplatin, mytomycin, and bleomycin were used with a total radiation dose of 5,000 rads. The toxicity of the four drugs was found to be excessive. Four patients (20%) needed a salvage operation. One patient survived 5 years [5]. The number of patients in this ongoing study is still too small to allow conclusions, but the numbers to date illustrate another heated controversy. Some authors [6] advance the traditional anatomical viewpoint that a more extensive resection of the esophagus and periesophageal tissues leads to the best available cure rates and local control. Other investigators [5] claim that more extensive chemotherapy and irradiation provide the best chance for cure; they advocate reserving operation for patients who cannot tolerate the chemotherapy or who did not achieve a complete response or who have dysphagia from a stricture resulting from the irradiation. This controversy remains unresolved.

The results of the combination of chemotherapy and radiation treatment on esophageal cancer are seriously challenging the traditional therapeutic approach to this disease. However, the prolonged hospitalization, the cost, the morbidity and mortality related directly to chemotherapy and radiation therapy, and the reported progression of the disease during the treatment are contested points and may cause one to eschew this innovative mode of treating esophageal cancer [7].

Some studies seriously question the value of preoperative chemotherapy. In a nonrandomized study, Parker and co-workers [8] compared results of treatment of esophageal cancer with chemotherapy-irradiation and operation to a historical series of patients pretreated with irradiation alone before resection of the esophagus. The comparison showed no benefit from the added chemotherapy. Although Parker and co-workers question the long-term validity of multimodality therapy, they are continuing to explore this treatment "with undampened enthusiasm."

Multimodality treatment of esophageal cancer brings creativity and imagination to a field of medicine plagued with failure. A number of practical questions have been raised: What is the optimal treatment? Is multimodality treatment better than a more extensive resection? Should resection of the esophagus be done when a complete response was achieved? When a complete response was not achieved, should further chemotherapy and irradiation be given? What will be the complication rate of more chemotherapy and a higher radiation dose? What is the right sequence of treatment? Which are the most appropriate drugs? Are we approaching a time when operation for cancer of the esophagus will be reserved for patients who either cannot tolerate chemotherapy and irradiation or do not have a complete response?

Orringer and associates present strong evidence of a notable improvement over past methods. This may help to sweep us above the hopelessness to which these patients were previously condemned. The main drawback of this study and others is that the controls are historical. We need randomized, prospective, well-designed, and carefully conducted clinical investigation to resolve the controversies that remain. Although many investigators who have tried multimodality treatment may be reluctant to participate in studies that include the use of traditional treatment modes without chemotherapy, I urge physicians and surgeons who treat esophageal cancer to enter a substantial number of well-informed patients into properly designed protocols. This is necessary if pending questions are to be answered quickly.

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Changing Cardiothoracic Practice Patterns

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> The times, they are a' changing.
>
> Bob Dylan

A decade or so ago, a manuscript dealing solely with a statistical analysis of parameters affecting results of cardiac surgery would not have progressed beyond the initial pass across the editor's desk, especially if there were no accompanying drawings or photographs of surgical techniques. But times have changed, and rapidly so. Nowadays, outcome results have suddenly become very important and will have an impact on the socioeconomics of the practice of cardiothoracic surgery. McGrath and colleagues [1] have performed a very timely and invaluable service to thoracic surgeons by analysis and documentation in precise numbers of what we all know from a visceral standpoint but have not, until now, developed the raw data with which to confront governmental agencies, third party payors, business coalitions, and nonmedical statisticians.

See also page 410.

In the last 2 years of negotiations between the organized thoracic surgical societies and governmental bodies (eg, Physicians Payment Review Commission, Health Care Financing Administration, Congress) it has become painfully apparent that we need factual data to use for defense of our position of negotiating fair, reasonable, and appropriate reimbursement for our services. The use of vague general concepts without analytical basis no longer is persuasive to budget-minded bureaucrats in the present milieu of ever-increasing costs for health care.

McGrath and colleagues clearly document the changing profile of our everyday practice. Cardiac surgical cases have become increasingly more difficult and factors such as increasing age, increasing numbers of female patients, repeat operations, and more complex operations are shown to have increased in a parallel fashion to increased mortality rates (from 4% to 7%) during the study period from 1982 to 1985. A comparable study performed today would probably show a continuing trend upward of these data.

Lest we accept all of the conclusions presented as strictly economic factors, we have missed the point. The conclusions should help confirm in our own minds that the changing practice profile also poses increasing clinical challenges. We should continually strive to improve the mortality figures, knowing full well that, in general, today's patients are sicker and have more diffuse cardiovascular disease, more problems with other organ systems, and more difficulties associated with repeat operations or combined procedures.

Establishment of practice guidelines is currently in vogue and in demand by nearly all remunerative agencies. Knowledge of outcome results has become critical in local hospital quality evaluation and in contractual marketing of institutional services. However, as we continue to negotiate financial arrangements, based on studies such as that presented here, we should also use the conclusions of McGrath and colleagues to demonstrate to ourselves and to our colleagues that we are currently trying to improve morbidity and mortality statistics in the face of increasingly complex clinical material.

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Chemotherapy and Radiation Therapy Before Transhiatal Esophagectomy for Esophageal Carcinoma

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Recent efforts to improve survival in patients with esophageal carcinoma have combined both systemic and local therapy. From October 1985 to October 1987, 43 patients with local-regional esophageal cancer (adenocarcinoma in 21, squamous cell in 22) were treated with cisplatin, vinblastine, and 5-fluorouracil chemotherapy concurrent with 4,500 cGy radiation therapy for 21 days before transhiatal esophagectomy 3 weeks later. Two patients died of chemotherapy/radiation therapy toxicity. Forty-one completed preoperative chemotherapy/radiation therapy. At operation, 2 patients had incurable metastatic disease; 39 underwent transhiatal esophagectomy. Eleven patients had no residual tumor in the resected specimen for a 27% (11 of 41) pathological complete response rate. Preoperative chemotherapy/radiation therapy resulted in no increased perioperative morbidity as compared with our historical controls. One patient died postoperatively of an unrecognized brain metastasis (2% operative morbidity). At a median follow-up of 27 months, 20 patients (47%) are alive and clinically disease-free and 21 have died, 19 from progression of their carcinoma. The median survival time for all 43 patients is 29 months (Kaplan-Meier estimate), and cumulative survival is 72% at 12 months, 60% at 24 months, and 46% at 36 months. All 11 patients with a complete response are alive at a median follow-up of 36 months, and all are disease-free. The 2-year survival of 60% of this group as compared with 32% in our earlier patients treated with transhiatal esophagectomy alone suggests that intensive combined modality therapy improves survival in these patients. A randomized prospective trial is now in progress.

(Ann Thorac Surg 1990;49:348–55)

Esophageal cancer remains a lethal disease; 5-year survival rarely exceeds 20% [1, 2]. Because approximately 75% of these patients have either local tumor invasion or distant metastases that preclude cure at the time the disease is diagnosed, traditional therapy has been focused on providing expedient palliation of dysphagia with the lowest possible risk. Since 1976, transhiatal esophagectomy (THE) without thoracotomy and a cervical esophagogastric anastomosis have emerged as our preferred method of esophageal resection and reconstruction both for benign and malignant disease; the procedure avoids the morbidity of a thoracotomy and the devastating consequences of an intrathoracic esophageal anastomotic leak [3–5]. As our experience with THE has increased, a relatively large referral base has been established, and we have now performed nearly 500 of these procedures, approximately 350 for carcinoma. Our initial enthusiasm for THE was based on a clear perception of decreased postoperative morbidity and mortality for patients requiring resection for esophageal carcinoma. With an overall hospital mortality of approximately 5%, we are able to provide efficient palliation in the majority of our patients. Unfortunately, as we expected, long-term survival after THE, as after standard transthoracic resection, is seldom achieved; our overall 2-year survival is 32%, and our 48-month survival is only 17%. Our desire to achieve long-term survival and even potential cure in these patients has led us, like other investigators, to consider multimodality therapy for esophageal carcinoma.

For editorial comment see page 345.

Preoperative chemotherapy in the treatment of local-regional esophageal carcinoma was instituted by Kelsen and colleagues [6] at the Sloan-Kettering Memorial Hospital in New York and by Steiger and co-workers [7] at the Wayne State Medical Center in Michigan in the 1970s. Cisplatin drug combinations had a significant local effect on many of these tumors [8, 9]. The Wayne State experience with combined preoperative radiation therapy (RT) and chemotherapy [7, 10] stimulated other researchers to evaluate further such combination adjuvant therapy [11]. We conducted a trial of combined preoperative chemotherapy with cisplatin, vinblastine, and mitoguazone in 36 patients with both adenocarcinomas and epidermoid carcinomas, and 25 of these patients then underwent THE

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Table 1. Tumor Location and Cell Type: Multimodality Therapy for Esophageal Cancer[a]

Site	Adenocarcinoma	Squamous Cell Carcinoma	Total
Cervical	0	3	3 (7)
Upper thoracic	0	3	3 (7)
Midthoracic	1	10	11 (26)
Lower thoracic	20	6	26 (60)
Total	21 (49)	22 (51)	43 (100)

[a] Numbers in parentheses are percentages.

[12]. Substantial toxicity was experienced, and the mean survival time of 14 months did not differ significantly from the 12.5-month mean survival time in our 100 earlier patients treated with THE without chemotherapy [5]. Complete eradication of the tumor was achieved in only 4% of the patients, and in 40% local-regional recurrence developed in follow-up. Radiation therapy was therefore added to the chemotherapy in an effort to improve our results. This report reviews our experience with preoperative chemotherapy (cisplatin, 5-fluorouracil, and vinblastine) administered concurrently with RT before THE in patients with esophageal carcinoma.

Material and Methods

Between October 1985 and October 1987, 43 patients with esophageal carcinoma were treated with preoperative RT and chemotherapy followed by transhiatal esophagectomy without thoracotomy. This treatment proposal entitled "Concurrent chemotherapy and radiotherapy followed by transhiatal esophagectomy in local-regional esophageal cancer" was described in University of Michigan protocol No. 1885, approved by the University of Michigan Medical School Institutional Review Board on October 1, 1985. Included within this group of patients were 32 men and 11 women with an average age of 62 years (range, 35 to 76 years). There were two black and 41 white patients. Twenty-two (51%) of the patients had squamous cell carcinoma and 21 (49%), adenocarcinoma of the thoracic esophagus or cardia (Table 1). Of the adenocarcinomas, 12 were associated with Barrett's epithelium in patients with long-standing gastroesophageal reflux.

Of the 43 patients, 39 (91%) had experienced weight loss that ranged from 2.3 to 22.5 kg (mean, 7.7 kg). Tumor length varied from 1.5 to 3.0 cm in 11 patients (26%), from 3.5 to 5.0 cm in 8 (17%), from 6.0 to 8.0 cm in 13 (30%), and from 9.0 to 12.0 cm in 8 (17%). Three patients had totally obstructing tumors, the length of which could not be determined preoperatively. According to the 1983 American Joint Committee on Cancer staging criteria [13], 79% of the patients had a clinical T_2 primary tumor (lesion greater than 5 cm in length, circumferential or obstructing). Regional adenopathy believed to represent metastatic disease was evident on chest and abdominal computed tomographic (CT) scans in 24 (56%) of the patients.

Criteria for eligibility in this study included the following:

1. Newly diagnosed esophageal cancer without previous treatment
2. Patient believed to be an acceptable operative risk for esophagectomy
3. Tumor judged to be totally resectable (no evidence of distant metastases or tracheobronchial invasion)
4. Disease limited to the esophagus and regional lymph nodes such that it could be encompassed by a single (tolerable) radiation field
5. Karnofsky performance status of at least 60%
6. Adequate bone marrow reserve (white blood cell count greater than 3,500 cells/μL, platelets greater than 100,000/μL)
7. Adequate renal function (creatinine clearance greater than 50 mg/mL)
8. Informed consent from the patient.

Before entry into the study, all patients underwent the following staging examinations: chest roentgenogram, barium esophagogram, chest and abdominal CT scans, head CT scan, and bone scan.

The treatment plan consisted of in-hospital combined RT and triple-drug chemotherapy with cisplatin, vinblastine, and 5-fluorouracil for 21 days, followed by a 3-week rest, and then THE on approximately day 42. Cisplatin (20 mg/m^2/day) was administered by continuous intravenous infusion on days 1 through 5 and 17 through 21. To minimize renal toxicity, patients were prehydrated with normal saline solution, the total cisplatin dose was infused over 24 hours, and intravenous hydration was continued for the next four days. Vinblastine (1 mg/m^2/day) was administered by intravenous bolus on days 1 through 4 and 17 through 20. 5-Fluorouracil (300 mg/m^2/day) was administered by continuous infusion for the entire 21-day course of preoperative therapy.

A 10-MeV high-energy linear accelerator was used to administer RT. Simulation included the tumor as well as 5-cm longitudinal margins and 2-cm lateral margins. As indicated by pretreatment staging scans, the mediastinum as well as celiac or supraclavicular lymph nodes, or both, were treated using a three- or four-field technique, with patients in the prone position to increase the distance between the spinal cord and the esophagus. Our initial plan called for daily fractions of 250 cGy, five days per week, for a total of 3,750 cGy over 21 days. However, after the first 20 patients (10 with squamous cell carcinoma and 10 with adenocarcinoma), in an effort to further increase the histological complete response rate, we initiated hyperfractionated therapy, administering 150 cGy twice daily, five days per week, to a total dose of 4,500 cGy over 21 days. Spinal cord doses were kept at or below 3,000 to 3,250 cGy.

After completing the above 3-week in-hospital course of combined chemotherapy and RT, and after a 3-week rest, the patients underwent THE without thoracotomy as described previously [3, 5]. Alimentary continuity was established at the same operation, with the stomach mobilized into the posterior mediastinum in the original esophageal bed and anastomosed to the cervical esophagus. In one patient who had undergone a previous gastric resection for peptic ulcer disease, a short-segment colon interposition was required after resection of the tumor. A pyloromyotomy and feeding jejunostomy were standard. Accessible subcarinal, paraesophageal, and celiac axis lymph nodes were sampled routinely for staging purposes.

Statistical Methods

The BMDP1L program [14] was used to obtain product-limit estimates of survival times and to compare survival distributions. Log-rank (Mantel-Cox) test statistics are reported, although generalized Wilcoxon (Breslow) test statistics also were computed. In both comparisons, results of the generalized Wilcoxon tests were consistent with those of the log-rank tests. Preoperative characteristics of patients with negative pathology at operation were compared with those of patients with positive pathology at operation using Student's t tests (BMDP3D) for continuous variables and χ^2 tests for categorical variables (BMDP4F).

Results

Toxicity of Preoperative Therapy

Two patients died before undergoing operation of sepsis associated with bone marrow suppression. Hematological toxicity was common. Forty patients (93%) experienced leukopenia to a white blood cell count of 1,900/μL or less; 27 (63%) had febrile neutropenia; and 10 (23%) had thrombocytopenia to a platelet count of 49,000/μL or less. One third of the patients required blood transfusions to correct anemia induced by myelosuppression. Only 11 (26%) of the patients tolerated 100% of the planned dose of all three drugs; overall, the group received an average of about 85% of the ideal dose of each.

Anorexia and fatigue occurred in all patients. Nausea and vomiting were generally mild. The most serious nonhematological complication was radiation-induced esophagitis and associated odynophagia, which occurred in 37 patients (86%) and necessitated supplemental nutritional support in 34 (79%) (28 [65%] enteral and 6 [14%] total parenteral). Eight (19%) of the patients lost more than 10% of their initial body weight. No patient experienced renal or ototoxicity or peripheral neuropathy. In 2 patients, RT was not completed because of the development of severe radiation esophagitis. The other 41 patients received the scheduled total dose of 3,750 or 4,500 cGy without interruption.

Operation

Of the 41 patients operated on, 25 (61%) had operation within 1 week of the scheduled day 42 of the treatment plan; delayed recovery from bone marrow suppression or availability of operating time influenced the ultimate date of operation. The patients underwent operation an average of 50 days after initiation of chemotherapy and RT. One patient who attempted suicide at home after completing chemotherapy and RT required psychiatric treatment, and esophagectomy was delayed until day 77.

Two of the 41 patients operated on did not undergo an esophagectomy because of the finding of incurable disease at exploration: a hepatic metastasis in 1 and extensive prevertebral fascial invasion and involvement of the aortic arch and great vessels with an upper thoracic squamous carcinoma in the other. Thus, the overall operability rate in this series was 95% (41 of 43). Thirty-nine patients underwent THE. In 1 patient who had undergone a previous gastric resection for peptic ulcer disease, a short-segment colon interposition through a right thoracotomy was required to restore alimentary continuity after esophagectomy. In the other 38 patients, a cervical esophagogastric anastomosis was performed as described previously [15], using a single-layer 4-0 polyglycolic acid suture interrupted technique. In the majority of patients, THE was not believed to be technically more difficult because of increased periesophageal reaction from radiation and chemotherapy. On the contrary, some initially large tumors on barium swallow examination were so reduced in size or eliminated by preoperative therapy that the resection was believed to be technically expedited. Measured intraoperative blood loss in the 38 patients undergoing THE and cervical esophagogastric anastomosis averaged 832 mL (range, 220 to 3,000 mL), not significantly different from that of our previously reported THE patients who had no preoperative chemotherapy or radiation therapy [5]. A chest tube was required in 36 of the 38 standard THE patients because of entry into one or both pleural cavities.

Of the 39 patients undergoing esophagectomy, gross total removal of all visible or palpable tumor was believed to have been obtained in all but 1, in whom residual transmurally invasive tumor had to be fractured away from the prevertebral fascia. Unexpected residual disease was documented in 2 other patients. One patient with an upper thoracic squamous cell carcinoma was found on permanent histologic section of the esophagus to have a microscopic focus of carcinoma at the cervical margin. The other had a seizure 48 hours postoperatively, and a brain CT scan showed a metastasis. This patient was treated with high-dose steroids, developed an anastomotic leak, and died on postoperative day 42, the one postoperative death in this series (2% operative mortality). Routine preoperative staging with a brain scan in our patients was instituted after this experience. One additional patient in this group had a postoperative complication, small bowel obstruction at his jejunostomy tube insertion site leading to vomiting and an anastomotic leak that healed spontaneously after reoperation on the abdomen. No patient experienced recurrent laryngeal nerve paresis or paralysis or postoperative chylothorax. The length of postoperative hospitalization averaged 12 days and ranged from 10 to 52 days (the latter in the patient with the small bowel obstruction). Only 5 of the 39 esophagectomy patients were hospitalized longer than 12 days after operation.

Histopathological Stage Grouping

Histopathological assessment of the resected specimens indicated a complete response rate, ie, no residual cancer (T0 M0), of 27% (11 of 41), or 26% of all 43 patients entered into the study. The final TNM stage grouping for these

Table 2. Histopathological TNM Stage Grouping After Preoperative Radiation Therapy and Chemotherapy for Esophageal Carcinoma

Stage	No. of Patients
0 (T0 N0 M0)	11 (27%)
I (T1 N0 M0)	2
IIA	13
T2 N0 M0	7
T3 N0 M0	6
IIB	9
T0 N1 M0[a]	2
T1 N1 M0	0
T2 N1 M0	7
III	5
T3 N1 M0	4
T4 N1 M0	1
IV (TX N1 M1)	1
Total	41

[a] Two patients with no residual primary tumor, but with metastatic squamous cell carcinoma in regional lymph nodes, were staged as IIB.

patients based on the 1988 revised American Joint Committee on Cancer classification [16] is shown in Table 2. Thirteen patients (32%) were surgically staged as T0. Lymph nodes sampled for staging purposes were positive for metastatic tumor in 15 patients (37%).

Survival

The 2 patients who were operated on but did not undergo esophagectomy received palliative RT postoperatively. All other patients have been followed at regular intervals after operation without undergoing further treatment either until their death or to the present time. With a median follow-up of 27 months, 21 patients have died, 19 of their disease (2 from complications of myelosuppression) and 2 of other causes (myocardial infarction, hepatorenal syndrome). Twenty of the 43 patients (47%) are alive and clinically disease-free. In 15 of the 36 patients in whom "complete" resections were believed to have been achieved, the carcinomas recurred: locally in 1 patient with squamous cell carcinoma, at a distant site in 9 patients with adenocarcinoma and 3 patients with squamous cell carcinoma, and both locally and at a distant site in 1 patient with adenocarcinoma and 1 with squamous cell carcinoma.

The median overall survival for the group is 29 months (Table 3). Cumulative survival is 91% at 6 months, 72% at 1 year, 60% at 2 years, and 46% at 3 years. Although patients with adenocarcinomas appear to have a survival advantage over those with squamous cell carcinoma, the differences in survival distribution are not statistically significant ($p = 0.25$). For the purposes of comparison, surgical stage has been divided into two categories (Table 3): "no disease" (patients shown to be T0 N0 at operation) and "residual" (20 patients shown to have stage I, IIA, IIB, or III disease after treatment) (Table 2). The residual disease category has been further subdivided into patients with local disease confined to the esophagus (stages I and IIA) and patients with regional disease (regional lymph node involvement, stages IIB and III).

The 11 patients who had no residual disease at operation (T0 N0) are all still alive and disease-free; 1 underwent resection of a solitary brain metastasis 10 months after esophagectomy. Minimum follow-up time for these patients is 25 months, the median follow-up is 36 months. Their survival is clearly superior to that of patients with

Table 3. Survival After Chemotherapy and Radiation Therapy Combined With Transhiatal Esophagectomy for Esophageal Carcinoma[a,b]

Variable	n	Median Survival Time (mo)	Cumulative Survival (%)				Significance[c]
			6 mo	12 mo	24 mo	36 mo	
Overall	43	29 (d)	91 (4)	72 (7)	60 (8)	46 (8)	
Histological type							0.25
Adenocarcinoma	21	NR	100 (d)	86 (8)	67 (10)	52 (11)	
Squamous cell carcinoma	22	28 (13)	82 (8)	59 (10)	55 (11)	41 (12)	
Surgical stages[e]							0.0004
No disease (T0 N0)	11	NR	100 (d)	10 (d)	100 (d)	100 (10)	
Residual	30	23 (4)	93 (5)	67 (9)	49 (9)	29 (9)	
Local (I and IIA)	15	32 (6)	93 (6)	67 (12)	59 (13)	42 (14)	
Regional (IIB and III)	15	15 (12)	93 (6)	67 (12)	39 (10)	16 (11)	

[a] Survival calculated from date of diagnosis. [b] Numbers in parentheses are standard errors. [c] Mantel-Cox (log-rank) test for differences in survival distributions. [d] Could not be calculated. [e] Survival distribution of patients with no disease as compared with that of patients with residual disease. Two patients who died of complications from preoperative therapy are excluded.

NR = not reached; SE = standard error.

Table 4. Preoperative Characteristics

Variable	No Disease (T0 N0, n = 11)	Residual Disease (n = 30)	*p* Value
M/F	8/3	23/7	0.79
Age (yr)	62 (SE, 2)	59 (SE, 2)	0.36
KPS	83 (SE, 2)	87 (SE, 1)	0.10
Histology, adeno/ squamous	5/6	16/14	0.65
Location, cervical-mid/ lower	6/5	11/19	0.30
Length of tumor (mean, cm)	8.5 (SE, 0.7)	7.0 (SE, 0.7)	0.24

KPS = Karnofsky performance status; SE = standard error.

residual disease at operation ($p = 0.004$). These latter patients have a median survival time of 23 months, and their cumulative survival at 12, 24, and 36 months is 67%, 49%, and 29%, respectively. There is no statistically significant difference in survival distribution between patients with local disease and those with regional disease ($p = 0.13$).

To determine whether the superior survival of the stage 0 patients over that of the remaining patients was attributable to systematic differences in the stage 0 group at entry into the study, we assessed the importance of differences in demographic and clinical characteristics at baseline (Table 4). There was no significant difference between the two groups in age, sex, or performance status or in tumor histology, location, or size.

Comment

This report adds to the current wave of enthusiasm for multimodality therapy for esophageal carcinoma, a phenomenon that is likely borne of near-universal frustration with the results of conventional therapy using any single treatment option. The treatment plan described has several relatively unique features: administration of 5-fluorouracil as a continuous infusion for 3 weeks, the total dosage of cisplatin, use of vinblastine, RT administered in hyperfractionated (twice daily) dosage, and the standard operative technique—THE without thoracotomy. Since 1984, several published series have reviewed experience with preoperative chemotherapy for esophageal cancer [11, 17–20], and in nearly half of these, RT has also been administered, generally preoperatively (Table 5). Recent multiinstitutional nonrandomized trials [25, 26] have evaluated the Wayne State experience [28] with preoperative cisplatin, 5-fluorouracil, and RT. As with our patients, patients undergoing esophagectomy had a complete re-

Table 5. Preoperative Chemotherapy and Radiation Therapy for Esophageal Carcinoma

Reference	Year	Preoperative Drugs	Preoperative Radiation (rads)	No. Completing Preoperative Therapy	No. Undergoing Esophagectomy	Operative Mortality (%)	Complete Response Rate (%)	Survival After Resection (%)
Austin et al [21]	1986	DDP/5-FU	3,000	11	11	2.5	36.0	36 at 30 mo
Campbell et al [22]	1985	DDP/5-FU	3,000	21	15	20.0	14.0	52 at 24 mo
McFarlane et al [23]	1988	DDP/ 5-FU(SCC), DDP/5-FU/ Mito-C (Adeno)	3,000	22 (9 SCC, 13 Adeno)	19 (9 SCC, 10 Adeno)	10.5	36.0	66 at 24 mo, 33 at 36 mo
Popp et al [24]	1986	DDP/5-FU, 5-FU/ Mito-C, 5-FU/DDP/ Vincr	3,000	21	10	17.0	9.5	21 at 30 mo
Poplin et al [25]	1987	DDP/5-FU	3,000	102	55	11.0	18.0	14 at 36 mo
Seydel et al [26]	1988	DDP/5-FU	3,000	29	27	3.7	36.0	NA
Wolfe et al [27]	1987	DDP/ VP-16(SCC), DDP/5-FU (Adeno)	4,500	29 63	29 (17 SCC, 12 Adeno)	0	16.0	44 at 24 mo
Orringer [Present report]	1990	DDP/5-FU/ Vinbl	3,750 (21 patients), 4,500 (22 patients)	41	39 (20 SCC, 19 Adeno)	2.0	27.0	60 at 24 mo, 46 at 36 mo

Adeno = adenocarcinoma; DDP = cisplatin; 5-FU = 5-fluorouracil; Mito-C = mitomycin; NA = data not available in reference; SCC = squamous cell carcinoma; Vinbl = vinblastine; Vincr = vincristine.

sponse rate of 18% to 30%, but mean survival times were not improved; in patients undergoing resection mean survival was only 14 months in the Southwest Oncology Group study [25]. This contrasts with a mean survival time of 29 months in our own series. Although few studies of preoperative adjuvant therapy for esophageal cancer have evaluated adenocarcinomas as well as squamous cell carcinomas [23, 27], our results indicate that this treatment regimen is equally effective in both histological types and that the likelihood of having a T0 N0 response is not significantly different in the two groups.

Multimodality therapy has not yet been proven in a prospective randomized trial to result in improved survival in patients with esophageal carcinoma. Clearly, the price for such preoperative treatment is high and is measured in terms of toxicity, the need for prolonged preoperative hospitalization, and its physiological and psychological effects on an already weakened patient who must undergo a major thoracic operation. Despite this, we have not observed an increase in postoperative morbidity or mortality after pretreatment with RT and chemotherapy. Interdisciplinary cooperation and constant dialogue is required throughout the patient's treatment course. Endoscopic placement of a nasogastric feeding tube may be necessary in patients whose dysphagia worsens during therapy. Operating schedules must be coordinated with patients' completion of chemotherapy and RT, and flexibility must be maintained if a cancellation is required because of a persistently low white blood cell count. For most surgeons, this treatment is inconvenient and time-consuming. It represents a departure from the long-held tenet that the "best" treatment for esophageal cancer is an efficient esophagectomy and esophagogastrostomy that returns the patient to his or her family for the few remaining months of life. Yet any of us who have devoted years of professional life to the care of patients with esophageal cancer cannot help but be favorably impressed by the encouraging data that are emerging.

Skinner and associates have advocated an en bloc radical resection for potentially curable esophageal carcinomas as a means for improving survival. This extensive and meticulous dissection of the esophagus and surrounding mediastinal soft tissue may be viewed by some as the best, most aggressive "cancer operation" currently available for esophageal carcinoma. In a preliminary report of 80 radical esophagectomies [29], however, the 3-year survival rate of 24% was not appreciably different from the 22% rate we reported for THE without thoracotomy and no in-continuity lymph node dissection [5]. More recently, Skinner and associates [30] used their operation more selectively in 31 additional patients, one half with squamous cell carcinoma and one half with adenocarcinoma. The overall 1-year and 2-year survival in this group is 65% and 32%, respectively, as compared with our overall 1- and 2-year survival of 72% and 60%, respectively in patients undergoing multimodality therapy. The actuarial 3-year survival in the patients identified by Skinner and associates as those most likely to be benefited by the more radical resection (14 W1 N0 patients and 11 W1 N1 patients) was 71% and 55%, respectively. These results, although admirable, do not approach the 3-year survival of 100% in our T0 N0 patients. The logical explanation for the difference is that the latter group has had better local-regional control of their disease with multimodality therapy than can be provided by radical resection of the esophagus. This adds further support to the concept that biological behavior of the tumor, rather than magnitude of resection, determines survival in patients with esophageal carcinoma.

That one quarter of the patients we treated had no residual tumor in their resected esophagus or adjacent lymph nodes (T0 N0) and all of them are still alive and tumor-free with a median follow-up of 36 months cannot be a chance occurrence. The tumor-free survival of these patients appears to be a function of the preoperative therapy they received. If the apparent value of multimodality therapy in these patients is confirmed with prospective trials now underway, the challenge will then be to identify the predictive factors in the patient with esophageal carcinoma that indicate that a favorable response to such treatment is likely. Alternative treatment, perhaps immunotherapy, could then be offered to patients for whom expenditure of resources required for multidisciplinary therapy should be avoided.

The suggestion that esophagectomy be omitted in the treatment plan of the patient undergoing chemotherapy and RT for local-regional disease [31] is premature and unjustified. Unless an effective noninvasive means of detecting residual disease in the esophagus can be found, esophageal resection not only provides the ultimate means for assessing the effectiveness of therapy, but also offers the best means of providing local disease control and potential prolongation of life. At present, there is simply no method of clinical staging that insures the pathological findings, and as new variations of preoperative therapy for esophageal cancer emerge (as they surely will), careful histological assessment of the resected specimen will remain the "gold standard" for documenting effectiveness of therapy. The ultimate proof of the value of multidisciplinary therapy in the treatment of esophageal cancer awaits the results of a controlled, randomized study now underway. Nonetheless, these preliminary results add further support to the growing notion that the natural history of esophageal carcinoma can be altered, and that long-term survival, not just palliation, may be achievable in many patients with this disease.

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DISCUSSION

DR F. HENRY ELLIS, JR (Burlington, MA): I congratulate Dr Orringer and his associates for their contribution to the serious therapeutic dilemma that faces all of us who have tried to care for patients with cancer of the esophagus or cardia. It is quite obvious that current modalities of therapy leave much to be desired, and it is hoped that studies such as this will provide us with new insights that will improve our results.

To evaluate studies such as this, we must enumerate some of the pros and cons of neoadjuvant therapy as compared with operation alone. As reported in the literature, about a third of patients so treated, whether with chemotherapy alone or with chemotherapy and radiation therapy, will show a complete response. It is said that this form of treatment provides better local control of the disease, and those that are responders show evidence of increased longevity.

Are there any disadvantages? Neoadjuvant therapy certainly requires a longer period of treatment in which the patient is under the care of a physician or is hospitalized, sometimes as long as 4 months. The incidence of toxicity is substantial, and as yet, there has been no evidence of any increase in 5-year survival rate.

Now how do the results of Orringer and associates compare with what has been reported in the literature? They show approximately the same percentage of complete responders, close to a third. They do not mention much about local control of the disease, but longevity is somewhat increased, a median survival time of 29 months, which is slightly higher than in our patients with operation alone. Forty-six percent were alive at 3 years, though to be sure, this is a cumulative figure and not an actuarial one. How this figure relates to a historical control group that had a poorer survival is difficult to say.

There are some negative features to the study. The period of therapy is prolonged (2 months in this series), though it is somewhat less than other reports of preoperative chemotherapy and radiation therapy. Toxicity was considerable, with a 4.7% mortality, double the surgical mortality, and only one quarter of the patients were able to complete the adjuvant therapy as originally designed. Whether long-term survival is better than after operation alone has not been answered by this study. Results of the proposed prospective randomized study may provide the answer.

For the sake of comparison, let me briefly relate our results with operation alone. 82.3% of our patients were operable and their resectability rate was close to 90%, with a 30-day mortality rate of 2.3%. The 5-year survival for curative resections was 23.3% and close to 34% as 3 years, lower to be sure than the 46% Orringer and associates report but their figures are cumulative, not actuarial, and are difficult to compare.

In conclusion, I would like to ask Dr Orringer two questions: Why do you not proceed with palliative resection in the face of a metastatic deposit in the liver? I have found a doubling of the expected survival rate in such patients with excellent palliation of dysphagia.

Finally, as it is quite clear from this study and from others that the "complete" responders do much better than nonresponders, what steps are you taking to determine some way to identify those patients who will be complete responders before initiating this form of treatment for everybody, two thirds of whom will probably not benefit from it?

DR ORRINGER: As usual, Dr Ellis has targeted the key questions here. I think we are entering a new and exciting time in the treatment of this disease. We have seldom before been able to talk about such a group of patients with esophageal cancer in which 27% are alive with no residual disease that can be detected at 3 years. It truly seems that the natural history of this disease can be altered in certain patients.

But what is different about those patients who have responded to preoperative neoadjuvant therapy and those who have not? This is where the new areas of cancer investigation are going to play a role, and this information, I believe, will change our basic approach to these patients.

For example, we may soon be routinely assessing preoperative biopsy specimens for deoxyribonucleic acid content of the tumor cells with flow cytometry or evaluating other characteristics of the tumors at a cellular level using immunological tools. The results of the present study have stimulated us to begin a prospective randomized trial, and there is a need to utilize other diagnostic modalities such as esophageal ultrasound to help us differentiate those patients who are suitable for the type of multimodality therapy we have described from those in whom this treatment is ineffective and some alternative therapy is indicated.

Patients who have spread of their cancer beyond the confines of the esophagus, to the liver or distant spread, are staged according to the current TNM staging as having stage IV esophageal cancer. In our experience, the majority of those patients live 6 months or less, and we are hard pressed to recommend major resectional therapy for patients with such advanced disease. So I do not share Dr Ellis' enthusiasm for going ahead with resection in the face of a hepatic metastasis. I do not feel that the effort is justified by the small reward gained and the increased morbidity such patients with advanced disease often experience.

Multimodality therapy of esophageal cancer appears to be a "new frontier" area, and I hope to bring you follow-up on a prospective, randomized study, which really must now be done. I want to emphasize that our report today represents but another uncontrolled, unrandomized study, the conclusions of which do not justify establishing multimodality therapy for esophageal carcinoma as "state of the art" in the treatment of this disease.

Perhaps one other word of caution is indicated here. A number of investigators have favored multiinstitutional studies of multimodality therapy for esophageal cancer, as few institutions can accumulate enough patients quickly to reach useful conclusions about the efficacy of specific therapy. But even in talking with some of my colleagues here it becomes clear that there is a tremendous difference in radiation therapy techniques from one institution to another. Our radiation therapists, for example, utilize a very innovative three-dimensional CT dosimetry planning system that allows precise delivery of radiation with much less scatter and toxicity. This may explain why our patients have not experienced an increase in pulmonary toxicity after preoperative irradiation and chemotherapy, which some of our colleagues have seen in their patients. Radiation therapy, chemotherapy, and surgical techniques vary widely between institutions. So we have to be careful in generalizing from single papers that this is the way to go for all. The answer will come from the badly needed prospective, randomized studies that are currently under way.

Implantable Rate-Responsive Counterpulsation Assist System

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To apply the potential energy source available from skeletal muscle in cardiac assistance, we developed an implantable counterpulsation assist system. This study reports the results using this implantable counterpulsation assist system in an acute in vivo animal model. Twelve dogs had a dual-chambered, extraaortic counterpulsation pump anastomosed in parallel to the thoracic aorta. The left latissimus dorsi muscle was used to power the pump. A newly developed implantable stimulator was used to make the muscle contract in synchrony with the diastolic phase. The unique feature of this stimulator is its ability to adjust timing of muscle contraction according to changing heart rates. The stimulator is also able to detect arrhythmias, and as a safety measure, shuts down until a normal rhythm is resumed. During counterpulsation assist with the implantable counterpulsation assist system, diastolic pressure increased an average of 34 mm Hg from baseline, equivalent to a 69% augmentation. Systolic peak pressure decreased an average of 10 mm Hg, equivalent to an 11% unloading. With induced heart rate changes, the implantable counterpulsation assist system readjusted its timing, maintaining optimal counterpulsation without systolic interference. Induced ventricular tachycardia resulted in immediate shutdown of the stimulator until resumption of a normal rhythm. The feasibility of using an intraaortic balloon pump console as back-up was also demonstrated. Excellent counterpulsation was obtained with either muscle power or balloon pump console. We conclude that the implantable counterpulsation assist system can provide effective counterpulsation assist and has the potential for continuous cardiac support.

(Ann Thorac Surg 1990;49:356–62)

Circulatory counterpulsation with the intraaortic balloon is a widely accepted form of cardiac assist. Recently, reports of extended support with the balloon pump have confirmed its efficacy in the chronic situation [1–4]. In several cases, patients were supported from weeks to almost a year. Many more patients with end-stage failure could benefit from chronic counterpulsation support. A major limitation is the patient's dependency on an external power source with its risk of infection and restriction in mobility. A totally implantable counterpulsation assist system would offer an important therapeutic option for patients with end-stage heart failure.

Recent advances in technology and skeletal muscle biology now allow for a viable alternative source in cardiac assistance [5, 6]. It has been demonstrated that skeletal muscle can be made fatigue-resistant and powerful enough to continuously assist the heart [7]. We have attempted to apply this autologous power source to a totally enclosed circulatory support system. The main purpose of this investigation was to evaluate the efficacy of our implantable counterpulsation assist system (ICAS) in an acute in vivo model.

Material and Methods

Extraaortic Dual Chambered Pump

The muscle-driven counterpulsation pump used in this study is as previously described except for some slight modifications [8]. The inner blood sac of the chamber consists of a silicone bladder located within a rigid cylindrical housing. The outlets of the pump were 12 mm in diameter. The pump was powered pneumatically by the left latissimus dorsi muscle through compression of a bulb connected to the pump with Silastic (Dow Corning Corp, Midland, MI) tubing (Fig 1). A port in the Silastic tubing allows optional connection to an intraaortic balloon pump console.

Muscle Stimulator

A new, microprocessor based, implantable pulse generator (Prometheus) was provided by Medtronic, Inc (Minneapolis, MN) [9]. This unit has a built-in microcomputer that is programmed through telemetry with software operated on an IBM-compatible personal computer. In our study, software developed by Medtronic in collaboration with us for synchronized counterpulsation was programmed into the stimulator. It allows for pulse burst stimulation of the muscle, synchronized to the cardiac R wave. Timing for onset delay of the pulse burst and its duration period is adjusted automatically by the stimulator according to the varying RR interval that occurs with heart rate changes. In addition, adjustment of the pulse

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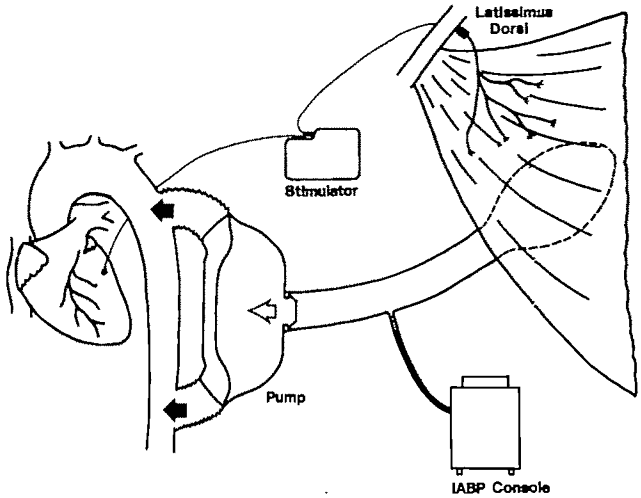

Fig 1. Schematic representation of implantable counterpulsation assist system. A dual-chambered pump is anastomosed in parallel to the descending thoracic aorta. The latissimus dorsi contracts on a pneumatic bulb displacing a silicone membrane in the pump. The stimulator coordinates muscle contraction with the cardiac rhythm. An intraaortic balloon pump (IABP) console can be attached as an alternative source of power.

voltage, frequency, and assist ratio can be easily made on the personal computer and sent via telemetry. A safety feature available with this pulse generator is an automatic shutdown of stimulation should any cardiac arrhythmias occur.

Twelve mongrel dogs of approximately 30 kg were induced with pentobarbital and maintained under 0.5% to 1% halothane endotracheal anesthesia. Through a left thoracotomy, the descending thoracic aorta was exposed, and a dual-chambered pump was anastomosed in parallel to the vessel with 12-mm Dacron grafts. Heparin (100 U/kg) was infused to partially anticoagulate the animal. A collapsible bulb was placed underneath the left latissimus dorsi, and the bulb was connected to the pump with Silastic tubing. The left thoracodorsal nerve was dissected free from the neurovascular bundle, and a bipolar neural cuff lead was placed around it. The lead was then connected to the stimulator. For sensing, epicardial leads were attached onto the myocardium and connected to the stimulator. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985) and the Canadian Council on Animal Care.

The stimulator was programmed to deliver pulse bursts of 2 V, 33 Hz frequency, and a pulse width of 210 μs. The delay period between triggering R wave and onset of stimulus was set to equal 30% of the RR interval, whereas duration of the stimulus was set to equal 60% of the RR interval (Fig 2). These parameters offered optimal timing and contraction force of the muscle for counterpulsation assist. The assist ratio during the studies ranged from 1:1 to 3:1. A Millar catheter (Millar Instruments, Houston, TX) pressure transducer was inserted through the left carotid artery into the aortic arch for hemodynamic monitoring.

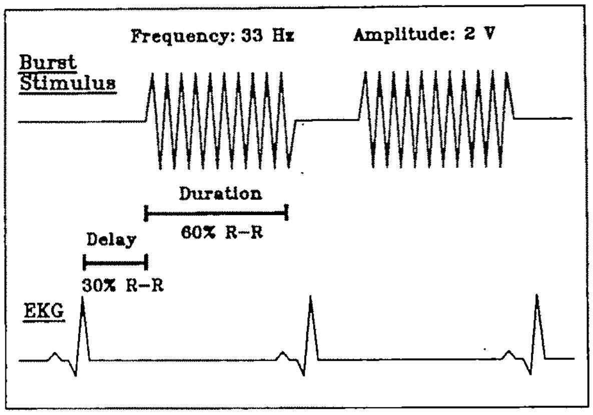

Fig 2. Parameter settings of the muscle stimulator. The burst pulses were set at 33 Hz frequency and 2 V amplitude. Timing of the bursts was determined by the sensed RR interval of the electrocardiogram (EKG). Delay interval between triggering R wave and burst onset was equivalent to 30% of the RR interval. Duration of burst was 60% of the RR interval.

Studies were performed with the stimulator on and off to observe the effects of counterpulsation on arterial pressure. Each animal served as its own control for comparison. The change in diastolic and systolic pressures were compared using paired *t* tests for significance. To evaluate the system's capability to track at different heart rates, esmolol or isoproterenol, or both, was infused as needed to vary the rhythm. The original stimulator settings were maintained throughout these rate changes, and arterial pressures were continuously monitored. The system's response to acute cardiac dysrhythmias was also tested in 2 dogs. While undergoing counterpulsation assist, the surface of the heart was manually irritated, inducing ventricular ectopy. The response to this insult was monitored continuously throughout the episode. Finally, we tested the feasibility of using an intraaortic balloon pump console (Datascope 82, Paramus, NJ) to drive the dual-chambered pump in 1 dog. This was achieved by connecting the gas outlet of the console to a side port of the Silastic tubing, which connects the pneumatic bulb to the pump (Fig 1). By temporarily clamping and excluding the pneumatic bulb from the system, we were able to drive the extraaortic pump with 40- to 50-mL gas volumes from the console.

Results

Hemodynamic Counterpulsation

Arterial counterpulsation was observed in all 12 dogs. A typical tracing obtained with the ICAS is shown in Figure 3. Diastolic pressure increase ranged from 20 to 50 mm Hg

Table 1. Pressure Results in 12 Dogs

Pressure	Off	On	Augmentation
Diastolic (mm Hg)	51.3 ± 14.3	83.0 ± 15.5[a]	34 (69%)
Systolic (mm Hg)	85.8 ± 14.2	77.1 ± 12.3[a]	−10 (−11%)

[a] Significance: $p < 0.001$ versus pump off.

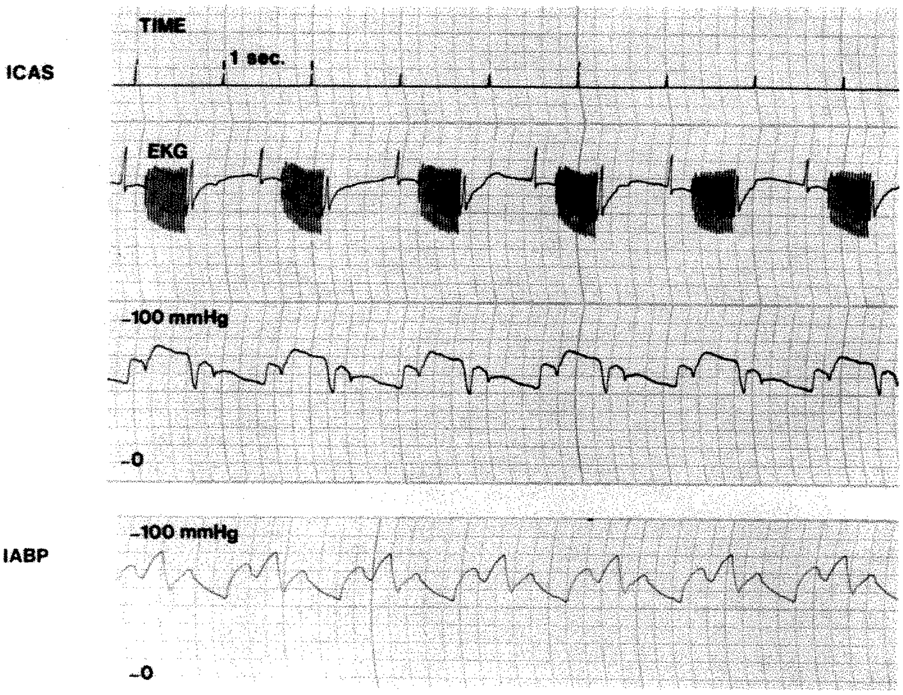

Fig 3. Representative arterial tracing with the implantable counterpulsation assist system (ICAS) compared with that with an intraaortic balloon pump (IABP). Assist ratio for both systems was set at 1:2. Note the burst artifact from the muscle stimulator at every second beat in the electrocardiographic (EKG) tracing.

(Fig 4). The mean increase was 34 mm Hg, which represented a 69% increase from baseline. Systolic pressure decrease ranged from 0 to 20 mm Hg (Fig 5). The mean decrease was 10 mm Hg, which represented a 10% decrease from baseline. When analyzed by the paired *t* test, both diastolic and systolic changes were significant ($p < 0.001$) (Table 1).

Heart Rate Changes

By using a β-blocker (esmolol) and a β-agonist (isoproterenol), heart rate changes from 70 to 194 bpm were obtained. Throughout this range, good counterpulsation was maintained without any need for timing adjustment of the stimulator. At no instance was there any systolic interference seen from mistimed counterpulsation. Tracings from a dog in which heart rate was varied while undergoing counterpulsation are shown in Figure 6.

Arrhythmia

In 2 dogs, ventricular tachycardia was induced by mechanical irritation of the heart during counterpulsation. In both instances, the stimulator immediately shut down and resumed function only after a normal rhythm was reestablished. No systolic interference was observed during this period of arrhythmia. A tracing during this period of arrhythmia is demonstrated in Figure 7.

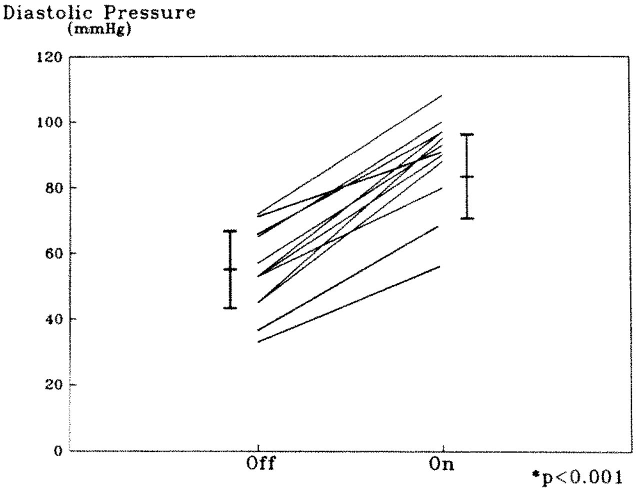

Fig 4. Comparison of diastolic pressures with the implantable counterpulsation assist system off and on. Error bars represent mean values ± standard deviation. The difference was statistically significant (p < *0.001 by paired* t *test). See Table 1 for further details.*

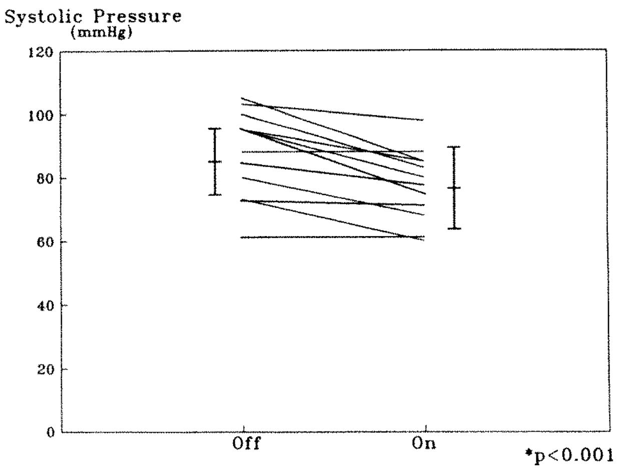

Fig 5. Comparison of systolic pressures with the implantable counterpulsation assist system off and on. Error bars represent mean values ± standard deviation. The difference was statistically significant (p < *0.001 by paired* t *test). See Table 1 for further details.*

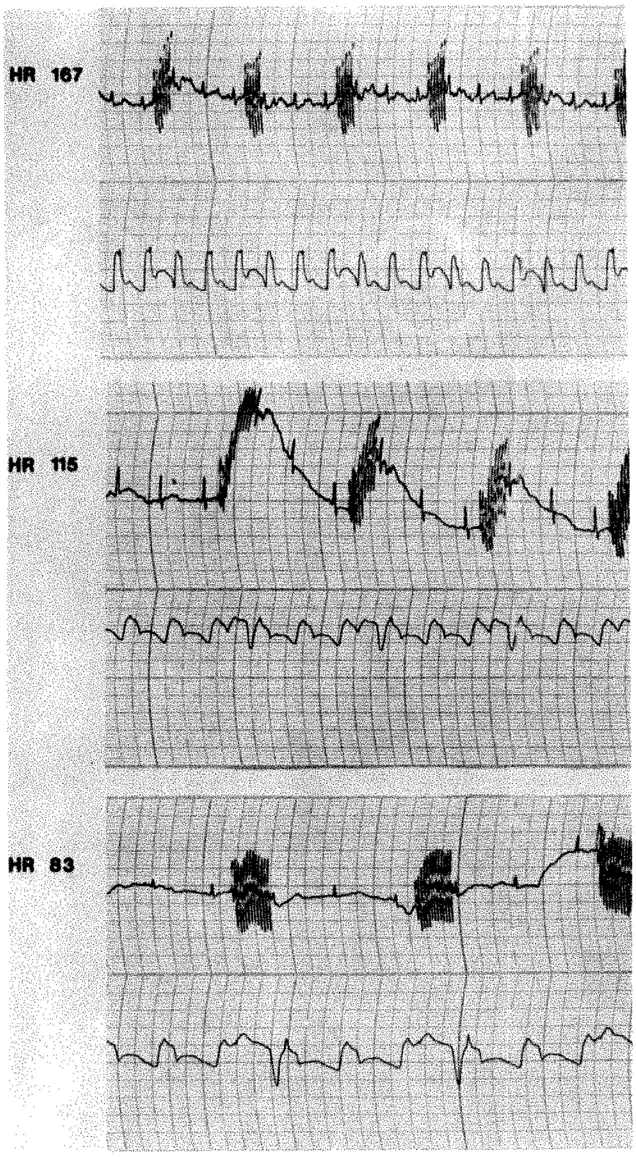

Fig 6. Electrocardiographic and arterial tracings at three different heart rates (HRs). Note as the heart rate decreases, the RR interval increases. Delay between onset of pulse bursts and duration of bursts also increase proportionately. Optimal timing of counterpulsation is maintained with no systolic interference.

Back-up Intraaortic Balloon Pump Console

In 1 animal, an intraaortic balloon pump (IABP) power console was hooked to the ICAS. Comparable counterpulsation assist was obtained with either the muscle or the IABP console. Tracings of these two modes of power source are shown in Figure 8.

Comment

In the late 1960s, Kantrowitz [10] began reporting the first successful clinical cases of intraaortic balloon pumping. Since then, the IABP has become the most extensively used form of circulatory assist. The physiological benefit of counterpulsation derives from the favorable balance between myocardial supply and demand through diastolic augmentation and systolic unloading [11, 12]. In our study, we attempted to emulate these effects of diastolic augmentation and systolic unloading with a muscle-powered ICAS.

Muscle-powered cardiac assist is now feasible because of two recently introduced concepts. They include the fact that skeletal muscle can be made fatigue-resistant for continuous work and that with pulse-train stimulation, enough force can be generated for effective cardiac assistance [13, 14]. Since the early 1980s, we have attempted to apply this biomechanical energy source in a counterpulsation assist system [15, 16]. In 1988, Kochamba and coworkers [8] introduced the concept of a dual-chambered extraaortic pump for skeletal muscle-powered counterpulsation. In our ICAS, we used a slightly modified version of this pump that provides improved hemodynamic flow and allows attachment to an IABP console. A stimulator (Prometheus) recently developed for the ICAS by Medtronic, Inc, provides synchronized contraction of the muscle with the diastolic phase of the cardiac cycle [9]. Using this new stimulator and the dual-chambered pump, we tested the ICAS in an animal model.

Our results demonstrate that the ICAS is capable of counterpulsation assist equivalent to the IABP. In every animal, significant diastolic pressure augmentation was achieved. Average diastolic augmentation was nearly 70%. In addition, peak systolic pressures were decreased by an average of 10 mm Hg. This is equivalent to the degree of systolic unloading reported in other studies on the intraaortic balloon [11, 17]. By reproducing the effects of the intraaortic balloon on diastolic/systolic pressure contours, the benefit of the ICAS can be inferred.

For a counterpulsation system to function independently, it must be able to adjust the timing according to changing heart rates. The newly developed Medtronic muscle stimulator serves this purpose [9]. With a built-in microprocessor, the stimulator adjusts the delay and duration intervals of its burst pulses according to the sensed RR intervals. Therefore, as the RR interval changes with heart rate, the stimulator senses these changes and adjusts the delay/duration intervals to maintain optimal timing. Through preliminary trials, we found that excellent counterpulsation could be achieved by setting the burst delay at 30% and burst duration at 60% of the RR interval. The determination of optimal timing of counterpulsation was made by visual inspection of the pressure tracings, where there was good diastolic augmentation starting near the dicrotic notch, associated with appropriate systolic unloading. All our tracings demonstrated these features. Throughout our study, we maintained this setting of 30%/60% in all animals. The consistently optimal counterpulsation obtained in every animal attests to the efficacy of this system. In some animals, heart rate changes were deliberately effected by infusion of either β-blocker or β-agonist. Automatic adjustments of delay and duration occurred, and optimal timing was maintained. We did not adjust the timing of stimulation with the different heart rates because the main advantage of the ICAS is its ability to automatically self-adjust according to spontaneous rate changes. Pressure tracings at various heart rates demonstrated that excellent counterpulsation had been maintained.

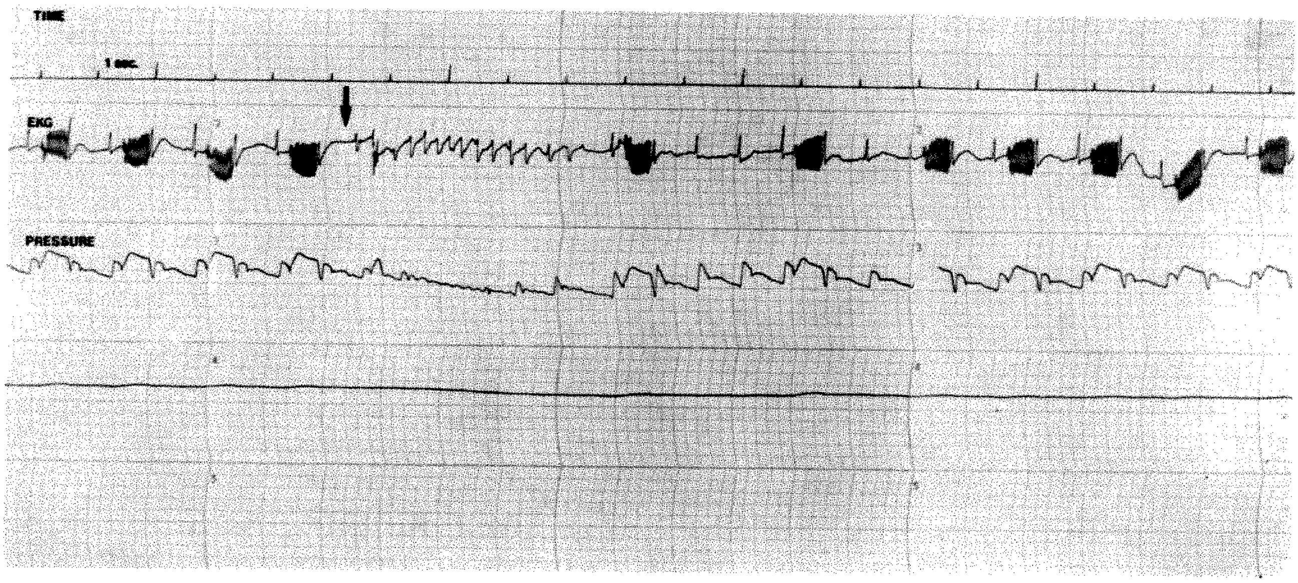

Fig 7. Response of implantable counterpulsation assist system to ventricular arrhythmia. Implantable counterpulsation assist system is providing assist at 1:2 ratio when ventricular tachycardia is induced (arrow). *The stimulator shuts down immediately and resumes function only after sinus rhythm is reestablished. No systolic interference is observed during this period.* (EKG = *electrocardiogram.*)

The stimulator possesses a safety feature against cardiac arrhythmias. With sudden large changes in RR intervals, as occurring in arrhythmias, the stimulator automatically shuts down until a more regular rhythm is reestablished. We studied this safety feature in 2 animals in which ventricular tachycardia was induced. In both instances, the stimulator promptly shut down on induction of the arrhythmia and resumed function only after a normal rhythm was reestablished. There was never any evidence of systolic interference due to mistiming during this period of arrhythmia.

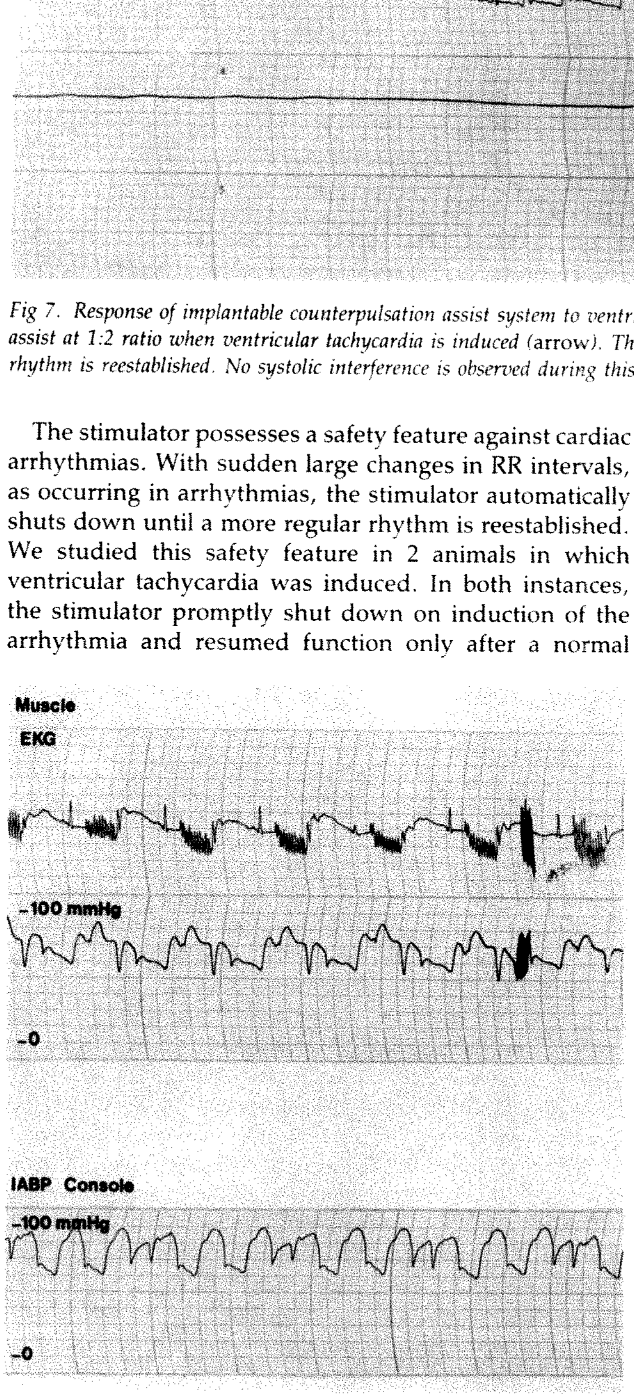

Fig 8. Comparison of counterpulsation obtained with either the muscle or the intraaortic balloon pump (IABP) *console. Equivalent assist is achieved with either system powering the pump.* (EKG = *electrocardiogram.*)

The main goal of the ICAS is to exploit the potential source of energy from skeletal muscle. However, the possibility exists for the muscle or stimulator system to fail. Should such a situation arise, it is important to have an accessible external back-up power source for the extraaortic pump. We determined the feasibility of using a readily available IABP power console to drive our extraaortic pump to maintain counterpulsation. With minor modification of the pneumatic system, we could easily attach a balloon console to drive the system. In 1 animal, we alternated driving the pump with either the muscle or the power console. Comparably excellent counterpulsation was obtained with either system. Therefore, effective back-up can be easily achieved with an IABP console for the ICAS. In addition, patients requiring immediate circulatory support would benefit from temporary console assistance to power the pump while their muscle undergoes transformation into a fatigue-resistant form.

With the recent advances in artificial assist devices, it is important to define a role for the ICAS. It is not our purpose to introduce the ICAS as a substitute for the ventricular assist devices presently being developed. We envision the ICAS as providing an alternative therapeutic modality in the wide spectrum represented by "end-stage" heart failure. At one end, there is the patient manageable with medicinal modes; whereas on the other end, we have someone requiring immediate dramatic intervention with a mechanical ventricle. In between these two extremes, there is the patient refractory to medical therapy but with residual function not requiring total ventricular support. This group of patients, in whom intermittent reports are being described of successful chronic IABP support, would benefit from a system like the ICAS. At this time, we are continuing with the chronic phase of the study in evaluating the ICAS and attempting to further refine its components.

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DISCUSSION

DR ADRIAN KANTROWITZ (Detroit, MI): First of all, if you are going to have a pumping chamber that is in parallel with the aorta and approximately the same diameter, presumably, then the flow through both the natural aorta and the parallel aorta will be reduced by half. That then raises the question of clotting on a long-term basis, and I think that is not a trivial problem.

Let me put it this way. I have been concerned with a device very similar to this and have been struggling with the clotting problem for about 25 years. Now, let's assume you are twice as smart as I am; this is a problem that you may have to think about for 10 years.

Second, presumably if you are going to have the possibility of plugging into an intraaortic balloon console, you are going to drive this with a gas such as air or helium. Does this imply that the transfer fluid in your system is a gas? If that were true, then you certainly could plug in an intraaortic balloon pump, but it is far more efficient to do this with a fluid, a liquid, in which case it would be difficult to plug an intraaortic balloon pump in. I appreciate your efforts and I do hope that you will continue with this.

DR LI: I think Dr Kantrowitz brought up several important points that we are dealing with. The issue that he first brought up was that of problems with thromboembolism in the pump. Right now we are proceeding with the chronic phase of the studies. Initially the problem was that we did not have an adequate stimulator, until now, that could provide optimal timing for counterpulsation. We have conducted some preliminary trials attempting to have chronic survivors with this system. The longest survivor we have had was for two days, and the problem is, as Dr Kantrowitz mentioned, that of thromboembolism. It is a problem that we are faced with and are trying to deal with. I do not know if I have the answers to this problem, but there is a lot of technology available out there, and hopefully we will be able to take advantage of some of that knowledge.

The second issue is what is the best medium to drive the system. Dr Kantrowitz stated that a fluid system would be much more efficient than a pneumatic system. We used air in our system, so we could easily attach a balloon pump console to it.

The argument that I have heard is that in a pneumatic system, air is compressible and therefore you lose a lot of energy as you try to "compress" the air. However, our system already has a resting pressure of approximately 60% to 70% of systemic pressure, and in that case the air is already compressed. We compared using fluid or air in this situation and found that the air actually provided better counterpulsation in that it evacuated the pump more quickly and provided better unloading, while providing equally good diastolic augmentation. Therefore, we prefer to use a pneumatic system.

DR KANTROWITZ: If you are going to fill the system with air, the air isn't going to stay there very long; it is going to leak out of whatever you seal it into. Therefore, you are going to have to have an opening on the outside to add more air. If you are going to do that, you might as well have the pump on the outside. And let met say that we have had some experience with intraaortic balloon pumping. In reviewing about 700 patients, we had about 20 patients who were treated long-term with balloon pumps, 20 to 71 days, and it was very discouraging. We could keep these patients on the balloon pump very well but the moment we sent them home, almost all of them died very rapidly in chronic heart failure. So, when the patient reaches that stage, he or she has to have more or less permanent support.

DR LI: I agree with the statement that a continuous leak of air is an issue in a chronic model. In the animals that we have attempted to keep for a long amount of time, we introduced a subcutaneous injection port in order to fill the system with air. We found that we needed to fill the system with air almost twice a day. That is a problem, and perhaps we can deal with better materials or eventually go to a fluid mechanism.

Our plan for this muscle-powered counterpulsation system is that it will be a permanent form of cardiac assistance. We envision in the future that the patient will be going home with the system functioning within him.

DR KANTROWITZ: Not so easy, not so easy.

DR W. GERALD RAINER (Presiding Officer): Nothing is.

DR JOHN A. JACOBEY (Mountain Lakes, NJ): My first question is, is excellent counterpulsation achieved when you do not increase the diastolic pressure to a point at which it is higher than the systolic pressure?

DR LI: My understanding of the physiology is that the higher the difference between aortic diastolic pressure and the left ventricular filling pressure, the better the coronary perfusion drive would be. So, in my opinion, I would think that optimally we would benefit from a system that could produce as much diastolic augmentation as possible.

DR JACOBEY: You may or may not be aware of our work in the past in which we showed diastolic pressures that were significantly higher than the systolic pressures, which I believe would be considered to be excellent counterpulsation. But, then, ours was an external device designed to have both systolic and diastolic effects and you are troubled with the difficulties of producing effects with internal apparatus.

And along that same line, my second question has to do with the placing of your device. Is this in the descending thoracic aorta or the abdominal aorta?

DR LI: It is in the descending thoracic aorta.

DR JACOBEY: So the pressure you apply to increase the diastolic pressure is a function of the volume and the rapidity of your device as it sits against the descending thoracic aorta, and then that pressure wave goes both distally and proximally so that by the time the pressure change reaches the coronary ostia, which is where you want to make that pressure change, there has been a great deal of diastolic expansion of the aortic wall. This leads to the question that arose in the report by Chachques and associates [1]. Isn't the reason why you would like to have those pressure changes made as near the coronary ostia as you can so that they do not have to travel through that much aorta and have that much dispersion of effect?

We have presented results of cannula counterpulsation, which was the type of counterpulsation done before the balloon, in which the cannula was inserted in the left subclavian artery and brought down to a point 3 cm from the aortic valve. When measuring pressure at the coronary ostia, not the aorta near where the intraaortic balloon is, we could produce diastolic pressures of 160 mm Hg and systolic pressures of 80 mm Hg.

DR LI: I agree with the positioning of the pump: the closer you get to the root, the more advantageous it would be. I think that if we put the pump closer to the root, we may be able to get better diastolic augmentation for coronary flow. Our results that you saw were made with tracings from a catheter located in the ascending root of the aorta.

DR GORDON N. OLINGER (Milwaukee, WI): I would like to pursue the question asked by Greg Misbach but not really fully answered from the paper by Chachques and associates [1], and that is the question of unloading.

Peak systolic pressure is really not a good indicator of unloading. We are more interested in isovolumetric systole during peak developed tension within the ventricle, and as I examined your tracings from animal to animal at various rates of augmentation and unloading, some of them seemed to indicate that you dropped end-diastolic pressure whereas others seemed to indicate that you did not.

Do you have any consistent pattern with respect to unloading as it relates to end-diastolic pressure, which is more a reflection of isovolumetric systole?

DR LI: The effect of systolic unloading from counterpulsation on myocardial oxygen consumption is difficult to measure. We used the peak systolic pressure because we believed it was the best index of myocardial oxygen consumption. By measuring peak systolic pressure, we did find significant decreases in pressure.

To consistently produce a presystolic dip is difficult with our system. There might be a slight variation in the RR interval between one and the next RR interval, and the system is unable to instantaneously adjust its burst duration to produce maximal unloading. This drawback is unavoidable because the stimulator depends on the previous RR interval to determine its burst duration.

DR CHIU: I am sure that when Dr Kantrowitz was doing his pioneering work in the 1960s, someone told him it could not be done, and if he had stopped doing it, he would not be honored here today as a pioneer. Certainly, there are still many questions remaining regarding this approach, but we will continue to address them the best we can.

The most important message in this paper is that the development of a totally implantable muscle-powered counterpulsation device requires a rate-responsive and arrhythmia-responsive muscle stimulator. This stimulator will be useful not only for our particular pump configuration, but also for others such as that reported by Chachques and associates [1]. Using the endogenous power source of transformed skeletal muscle for cardiac assist is still a young field, and at this point, we are still not sure what is the best way to use it. We are continuing to explore various possibilities and hope these efforts will lead to effective therapeutic modes applicable to patients in the years to come.

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Survival After Surgical Resection for High-Grade Chest Wall Sarcomas

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Indications for chest wall resection of metastatic or locally recurrent sarcoma and for subsequent bony reconstruction are controversial. Twenty-eight patients had chest wall resection for high-grade primary, metastatic, or recurrent sarcoma. In all patients, resection with selective reconstruction of the bony thorax was performed without operative mortality. Since 1980, only patients with four or more ribs resected have had selective bony reconstruction. Follow-up ranged from 8 to 132 months (median follow-up, 42 months). All deaths were related to sarcoma recurrence. The overall actuarial survival rate was 85% at 1 year, 65% at 3 years, and 59% at more than 5 years. The overall actuarial proportion without disease recurrence was 64% at 1 year, 52% at 3 years, and 40% at more than 5 years. There was no significant difference in overall or disease-free survival for patients with primary, metastatic, or recurrent tumors. The most important prognostic factors were positive margins and concomitant pulmonary resection for synchronous lung metastases. These data support aggressive resection to obtain pathologically tumor-free margins for chest wall sarcomas, whether primary, metastatic, or recurrent. Reconstruction can be individualized based on the extent of resection.

(Ann Thorac Surg 1990;49:363–9)

Sarcomas of soft tissue and bone account for approximately 1% of all malignancies. The chest wall is an uncommon site for sarcoma. Sixty percent to 70% of soft tissue sarcomas occur in the extremities with the remainder at other sites such as the trunk, retroperitoneum, head and neck, and breast [1, 2]. Primary neoplasms of the bony chest represent 7% to 8% of all intrinsic bony tumors [3]. Thus, few patients with chest wall sarcoma are available for evaluation.

Sarcomas involving the thorax can originate primarily within the chest wall, represent metastatic disease from a distant site, or develop as a local recurrence from a previously excised chest wall lesion. They occasionally develop in patients previously treated with radiation therapy for malignancies such as breast cancer or Hodgkin's disease [4, 5].

Aggressive chest wall resection for primary chest wall tumors including sarcomas is well described [3, 6, 7]. However, few data are available regarding the appropriate management of patients with metastatic or recurrent chest wall sarcoma. This report compares the results of aggressive treatment of patients with primary, metastatic, or recurrent chest wall sarcomas. Different prognostic factors for disease-free and overall survival were compared to see if such an aggressive approach for patients with metastatic or recurrent chest wall sarcomas is justified. We found no significant difference in overall or disease-free survival for patients with primary, metastatic, or recurrent tumors. Factors associated with perioperative morbidity and the need for formal chest wall reconstruction were analyzed. The effect of adjuvant radiation therapy and chemotherapy on patient outcome was examined, and overall management recommendations are made.

Material and Methods

The data analyzed originate from 28 patients undergoing resection of chest wall sarcomas in the Surgery Branch of the National Cancer Institute between April 1977 and January 1988. The diagnosis of high-grade sarcoma (grade II or III) was made by the Pathology Department of the National Institutes of Health using established histological criteria [8]. All patients were thought to have disease isolated to the chest wall on the basis of extensive preoperative staging. All patients included in this study were observed for a minimum of 8 months.

Surgical Technique

The surgical technique consisted of resection of the entire tumor in monoblock fashion with the aim of achieving pathologically negative margins by careful planning, assisted by intraoperative histological confirmation when in doubt. In all patients, full-thickness excision including the skin (if involved), subcutaneous tissue, and involved portion of the chest wall was performed. At least one uninvolved rib and the interspace above and below the tumor were included with the specimen whenever possible. There was no gross violation of tumor and no visible residual tumor in any patient. Adhesions between the chest wall and pulmonary parenchyma were handled by performing en bloc wedge resection ample enough to

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ensure tumor-free margins without removal of excessive parenchyma. The remainder of the lung parenchyma was carefully palpated for additional nodules, which were excised with tumor-free margins if present [9]. Selective reconstruction was performed using Marlex mesh, a muscle flap, or a Marlex mesh and acrylic "sandwich" [10] depending on the decision of the operating surgeon. Since 1980, only patients with four or more ribs resected have had selective reconstruction.

Radiotherapy

After chest wall resection, 9 adult patients with primary tumors were offered adjuvant radiation therapy as part of a prospective randomized trial for truncal sarcomas [11]. Patients with metastatic or locally recurrent sarcomas were selectively offered adjuvant radiation therapy. High-dose external-beam radiation therapy was administered using either a 6- or 10-MeV linear accelerator. Radiation volume was determined by review of the preoperative computed tomographic scan of the chest, the operative note, and radiopaque clips placed at the periphery of the operative field. The radiation volume was generally treated isocentrically by using obliquely directed fields determined at simulation. The initial volume was treated to 4,500 rads using 180-rad daily fractions followed by a cone-down boost of 1,800 rads, again using the 180-rad fractions. External-beam irradiation was initiated as soon as the wound was healed, usually within 3 to 4 weeks after operation. The exact techniques used in these patients have been discussed elsewhere [12].

Chemotherapy

Patients with primary chest wall tumors and adult histologies (n = 9) received radiotherapy and were randomized to receive or not to receive chemotherapy involving doxorubicin hydrochloride and cyclophosphamide in the Surgery Branch [11]. Doxorubicin, 70 mg/m^2, was administered every 28 days by intravenous bolus. Cyclophosphamide, 700 mg/m^2, was administered with doxorubicin every 28 days by intravenous drip over 30 minutes. A total of five cycles were given. Some patients seen early in the series received six cycles of high-dose methotrexate after maximum cumulative doses (500 to 550 mg/m^2) of doxorubicin were reached. Patients with metastatic or recurrent chest wall sarcoma of adult histology who had not previously received chemotherapy were offered a similar regimen.

Patients with pediatric histologies (osteosarcoma, Ewing's sarcoma, and other round cell tumors) (n = 8) were treated according to Pediatric Oncology Branch protocols. Those with primary tumors were generally treated with vincristine sulfate, doxorubicin, and cyclophosphamide preoperatively. Those with metastatic or recurrent tumors were offered additional chemotherapy whenever possible.

Patients who received chemotherapy in conjunction with radiation therapy had the first chemotherapy course three days before the initiation of radiation therapy. Subsequent courses of chemotherapy were administered during and after completion of radiation therapy.

Patient Follow-up

Outpatients were followed at 3-month intervals with complete physical examinations, blood chemistry studies, and chest roentgenograms. Full-lung tomography or computed tomography of the chest was performed every 6 months for 3 years and yearly thereafter. Outpatient follow-up was updated to September 1, 1988.

Statistical Evaluation

Actuarial survival and disease-free survival curves were plotted using the method of Kaplan and Meier [13]. Estimates of survival rates at specific time points were derived from these curves. Comparison of actuarial survival curves was performed using the method of Mantel and Haenszel [14]. All p values reported are two-sided.

Factors examined for possible association with time to recurrence and time to death were age at the time of resection, sex, classification of the tumor as primary versus metastatic versus recurrent, the logarithm of tumor volume, the number of ribs involved in resection, treatment with any chemotherapy, treatment with irradiation to the chest wall, postresection margin status, and pulmonary resection for synchronous lung metastases. Because of the long period of accrual of these patients, both a continuous factor (date of chest wall resection) and a dichotomous factor representing the era of resection (resection before 1983 versus resection in or after 1983) were also considered. Combinations of these factors were included in regression analyses using the Cox proportional hazards model [15]. Log rank (Mantel-Haenszel) tests of some individual factors were also performed.

Results

The 28 patients, 21 male and 7 female, ranged from 7 to 60 years old (median age, 29 years) at the time of resection. There were 14 primary chest wall sarcomas, 10 metastatic chest wall sarcomas, and 4 recurrent chest wall sarcomas. All tumors were classified as high grade (grade II or III), and included 20 adult soft-tissue sarcomas, 1 childhood rhabdomyosarcoma, 3 Ewing's sarcomas, 3 osteosarcomas, and 1 undifferentiated sarcoma. The 20 patients with adult histology were treated according to Surgery Branch protocols and the remaining 8 patients, Pediatric Oncology Branch protocols.

Thirty-day operative mortality was 0%. The mean postoperative duration of intubation was 1.2 days (range, zero to eight days). The Spearman rank correlation coefficient between duration of intubation and number of ribs removed was 0.5 ($p < 0.01$). The correlation between duration of intubation and need for reconstruction was 0.40 ($p < 0.05$). A total of 11 patients underwent chest wall reconstruction: 5 with Marlex mesh, 4 with a Marlex mesh and acrylic sandwich, 1 with a muscle flap, and 1 with Marlex mesh and a muscle flap. Since 1984, only patients with resection of four or more ribs have had reconstruction, with 38% (3/8) not undergoing reconstruction.

Complications occurred in 36% of patients and consisted predominantly of wound problems (Table 1). The most common wound problem was superficial skin necrosis. Wound complications were more common in patients

Table 1. Postoperative Complications

Complication	No.[a]
Wound problems	7 (25)
Deep venous thrombosis	1 (3.6)
Myocardial infarction	1 (3.6)
Grand mal seizure[b]	1 (3.6)
Total	10 (35.7)

[a] Numbers in parentheses are percentages. [b] This patient had a history of seizure disorder.

undergoing larger resections; 5 of 14 patients who had four or more ribs resected compared with 2 of 14 patients who had fewer than four ribs resected experienced wound complications. These differences were not significant, however (p = 0.19). The use of adjuvant or neoadjuvant therapy did not significantly increase the rate of wound complications. The wound complication rate was 33% in those who did not receive any additional therapy, 17% in those who received chemotherapy or radiation therapy or both preoperatively, and 37% in those who received chemotherapy or radiation therapy or both postoperatively. There were no major postoperative pulmonary complications such as pneumonia or respiratory failure.

Follow-up ranged from 8 to 132 months (median follow-up, 42 months). At last follow-up, 18 patients were alive, 13 without sarcoma recurrence. The site of first recurrence after chest wall resection was in the lung in 10 patients, the chest wall in 2 patients, the lung and chest wall in 2 patients, and the retroperitoneum (primary site) in 1 patient. The overall actuarial survival rate was 85% at 1 year, 65% at 3 years, and 59% at more than 5 years (Fig 1). The overall actuarial proportion with no disease recurrence was 64% at 1 year, 52% at 3 years, and 40% at more than 5 years (Fig 2).

The factor of overriding importance for survival and recurrence in these patients was margin status. Three patients (2 with metastatic disease and 1 with recurrent disease) had positive margins, and they had the three shortest survival times (5, 7, and 7 months), which was highly significant ($p < 0.001$). Margin status did not correlate with tumor type (primary, metastatic, and recurrent) or any other factors including tumor volume. Because all the deaths were due to sarcoma recurrence, margin status was the most important risk factor for recurrence as well. Having positive margins is estimated to increase the relative risk of recurrence by a factor of 8.3 (95% confidence interval, 1.8 to 38). Figures 3 and 4 show the actuarial curves of overall survival and freedom from recurrence stratified by margin status. Patients with negative margins had actuarial long-term survival and recurrence-free survival of 67% and 45%, respectively.

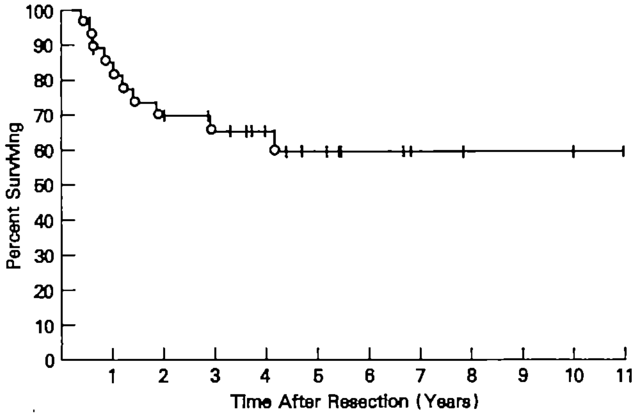

Fig 1. Actuarial curve of overall survival. The overall actuarial survival was 85% at 1 year, 64% at 3 years, and 59% at more than 5 years. The median survival has not yet been reached.

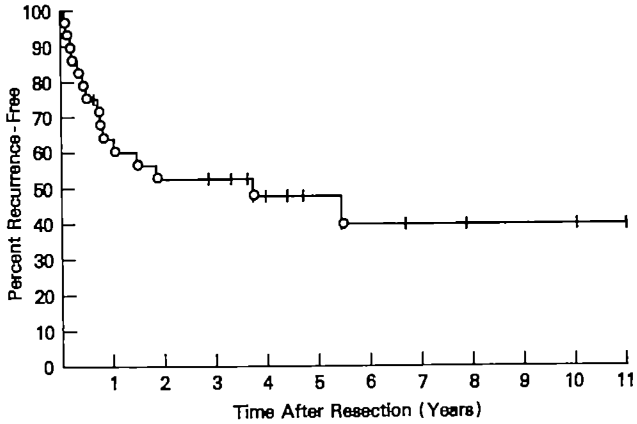

Fig 2. Actuarial curve of overall recurrence. The overall actuarial proportion free from recurrence was 64% at 1 year, 52% at 3 years, and 40% at more than 5 years.

No other factors were individually associated with survival or time to recurrence. Specifically, there was no significant difference between patients with primary, metastatic, and recurrent chest wall sarcomas in time to recurrence (Fig 5) and overall survival (Fig 6). In regression models, male patients operated on before 1983 seemed to be at higher risk with a significantly poorer

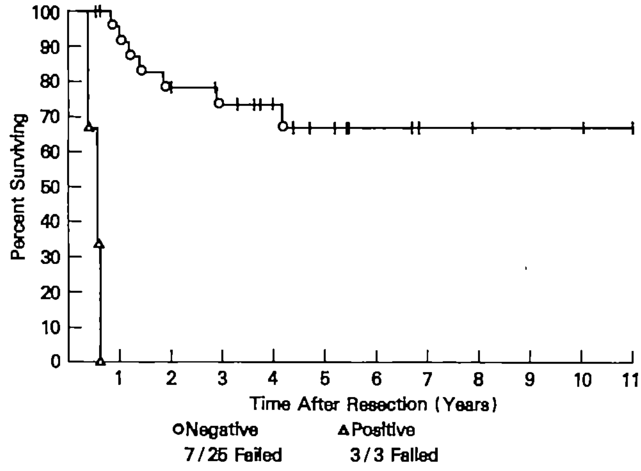

Fig 3. Actuarial curves of overall survival stratified by margin status. Patients with positive margins had a mean survival of 6 months. Patients with negative margins had a 67% survival at more than 5 years.

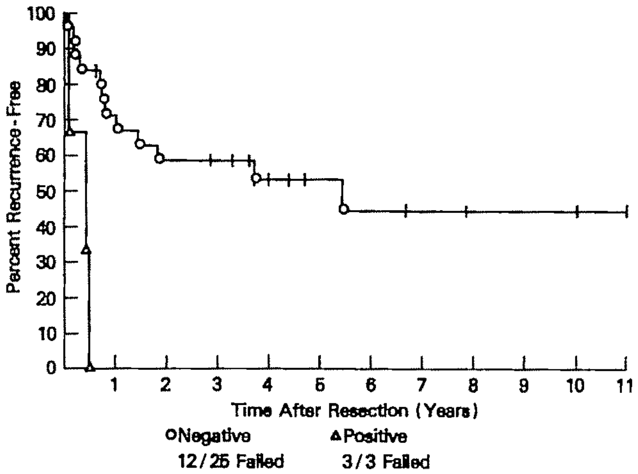

Fig 4. Actuarial curves of overall recurrence stratified by margin status. Patients with positive margins had a mean time to recurrence of 4 months. Patients with negative margins had a mean time to recurrence of more than 5 years.

survival (relative risk = 5.8, $p < 0.01$ for survival) and decreased time to recurrence (relative risk = 3.4, p = 0.01). It must be noted that the 3 patients with positive margins were all in this high-risk group. After the Cox model was adjusted for the effect of positive margins, there remained an increase in the risk of this group for time to recurrence and time to death, although it was of equivocal significance (relative risk = 3.7, p = 0.09 for survival; relative risk = 2.5, p = 0.13 for recurrence). After adjustments were made for both these variables, no other factor improved the fit of the model. This included the variables radiation therapy and chemotherapy. Chemotherapy (9 patients postoperatively and 6 both preoperatively and postoperatively) did not have a significant effect on survival of the entire group (Fig 7), and there was no improvement in survival seen in adults given chemotherapy when the pediatric subgroup was removed from the analysis.

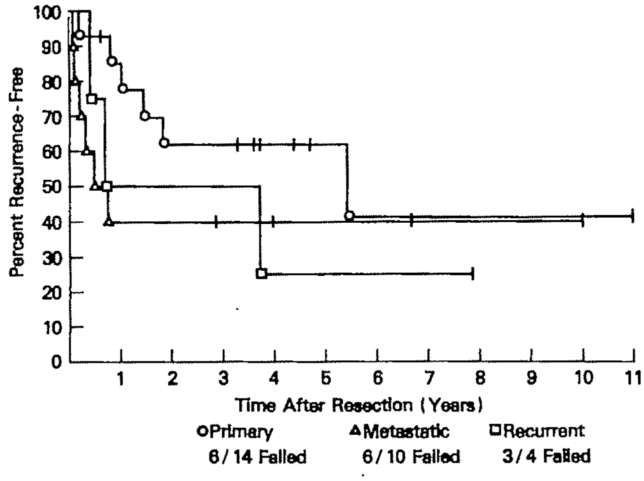

Fig 5. Actuarial curves of overall recurrence stratified by type of tumor (primary, metastatic, or recurrent). No significant difference was noted between the tumor types.

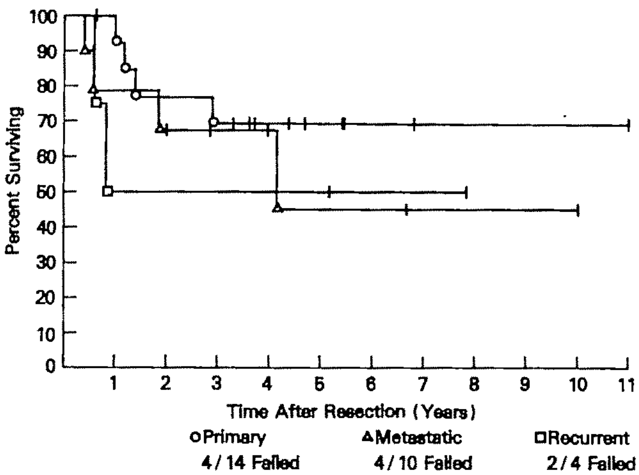

Fig 6. Actuarial curves of overall survival stratified by type of tumor (primary, metastatic, or recurrent). No significant difference was noted between the tumor types.

There was no significant difference in overall or disease-free survival between the adult and pediatric subgroups. With the pediatric subgroup removed from the analysis, the tests for other potential risk factors remained nonsignificant for the adult group except for pulmonary resection for synchronous metastases, which was associated with a significantly higher rate of recurrence (relative risk = 3.9, p = 0.03 by the likelihood ratio test) (Fig 8). Moreover, there was a significant decrease in the overall survival of those adults requiring pulmonary resection (p = 0.048) (Fig 9).

Comment

The role of chest wall resection in the management of primary chest wall tumors is well established. The indications for chest wall resection in the patient with locally recurrent chest wall sarcoma or sarcoma metastatic to the chest wall are less clear. Several large series [3, 6, 7] did

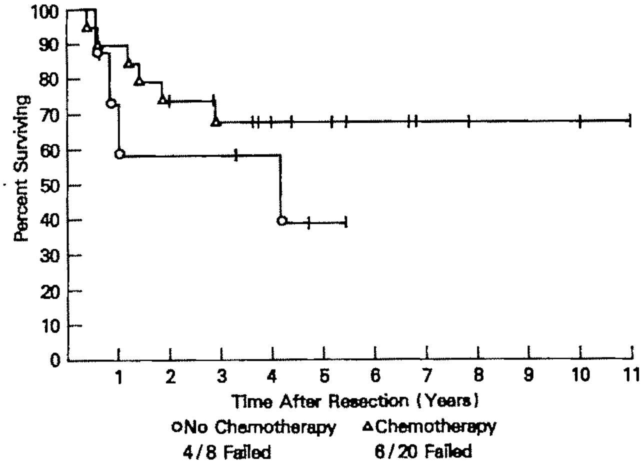

Fig 7. Actuarial curves of overall survival stratified by chemotherapy status. No significant difference was noted between patients who received chemotherapy and those who did not.

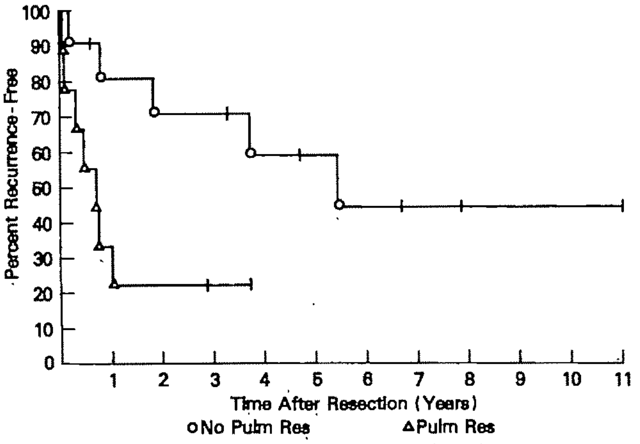

*Fig 8. Actuarial curves of overall recurrence in adults stratified by need for pulmonary resection (*Pulm Res*) for lung metastases. Those with pulmonary metastases at the time of chest wall resection, even if resection was complete, had a significantly higher recurrence rate (*p = 0.03*).*

not include patients with chest wall sarcoma due to local recurrence or metastatic disease. Others [10, 16] have shown a role for palliative resection of sarcoma metastatic to the chest wall, although no apparent survival benefit was noted.

In the series reported here, there was no significant difference in disease-free survival or overall survival of patients with primary, locally recurrent, or metastatic chest wall sarcomas. The disease-free survival of 40% at more than 5 years and overall survival of 59% at more than 5 years compare favorably with the overall survival of approximately 50% reported by Graeber [6], Sabanathan [3], and their associates for primary chest wall neoplasms and the disease-free survival of 51% reported by Greager and colleagues [7] for primary chest wall sarcomas. Our results differ from those of Pairolero and Arnold [16], who noted at median follow-up of 31.5 months a survival of 79% for patients with primary chest wall sarcomas and 33% for those with metastatic chest wall sarcomas, findings due most likely to the short follow-up and the inclusion of low-grade sarcomas in their analysis. McCormack and co-workers [10] reported a 5-year survival of 16.7% for patients with primary chest wall sarcomas and 10% for those with metastatic chest wall sarcomas.

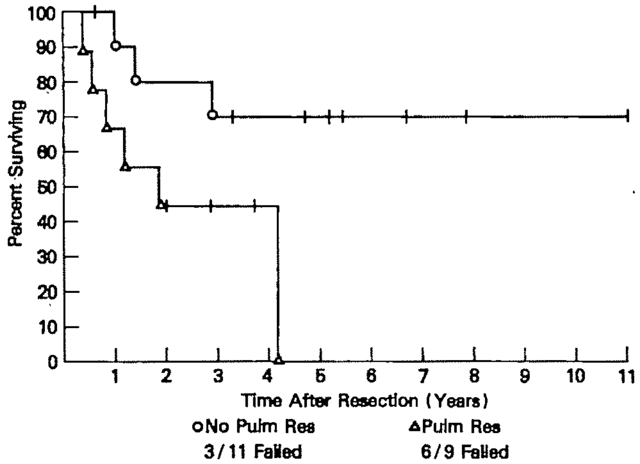

*Fig 9. Actuarial curves of overall survival in adults stratified by need for pulmonary resection (*Pulm Res*) for lung metastases. Those with pulmonary metastases at the time of chest wall resection, even if resection was complete, had a significant decrease in survival (*p = 0.048*).*

Although chest wall resection remains a formidable procedure, it can be performed with low morbidity and mortality, as we and others [3, 6, 7, 16, 17] have shown. In our series, postoperative intubation duration correlated with the extent of chest wall resection. The majority (79%) of patients were removed from ventilatory support in the operating room or by the following morning. However, our population is highly skewed toward the younger age group (mean age, 29 years), and hence most of the patients did not have preexisting pulmonary parenchymal disease.

Also unclear are the precise indications for reconstruction of the skeletal defect. Of 155 patients who underwent chest wall resection at Memorial Sloan-Kettering Hospital [10], 39 required muscle and skin closure alone for a small defect, 8 had closure with ox fascia, 94 had closure with Marlex mesh, and 12, with a Marlex mesh and methyl methacrylate sandwich. The remaining two patients, seen early in the series, had autotransplantation of rib and clavicle. Pairolero and Arnold [18] recommend that, in general, full-thickness skeletal defects of the sternum or lateral thoracic wall be reconstructed with prosthetic material. We have not observed any morbidity or mortality when we have not formally reconstructed defects involving fewer than four ribs.

A large number of factors were examined to see if they related to prognosis. The most important factor affecting both disease-free survival and overall survival was margin status, a finding emphasizing the importance of attaining negative margins by a carefully planned procedure, including intraoperative histological confirmation when in doubt. The only other factor significantly affecting the prognosis in adults was the presence of synchronous pulmonary metastases discovered at the time of chest wall resection. Patients with associated pulmonary metastases were found to have a higher chance of recurrence and decreased survival compared with those without pulmonary metastases, despite resection of all disease. That 9 adult patients in our series had pulmonary metastases not discovered during preoperative staging is not surprising. In a recent series of sarcoma patients, only 50% of the nodules found at thoracotomy were seen preoperatively on computed tomography [9].

The role of adjuvant chemotherapy in the management of sarcoma is controversial. One study [19] suggests that adjuvant chemotherapy with doxorubicin and cyclophosphamide with or without methotrexate prolongs disease-free survival and may prolong overall survival in patients with extremity sarcoma. The benefit for patients with truncal sarcoma is less clear [11]. Our study failed to show any benefit from chemotherapy given to the entire group having chest wall resection. When the patients were stratified according to adult or pediatric histologies, the adult patients still failed to show any benefit from chemotherapy. The results of our study must be interpreted with caution, however, because of the heterogeneity of the population, differences among the chemotherapeutic agents used and the timing of delivery, and the concomitant use of radiation therapy.

We believe that aggressive chest wall resection to achieve negative margins should be performed in patients with primary, locally recurrent, or metastatic sarcomas of the chest wall if preoperative staging shows no other disease foci. Bony reconstruction can be individualized based on the extent of resection. There is no significant difference in disease-free or overall survival among patients with primary, metastatic, or locally recurrent tumors. The most important prognostic factors are margin status and, in adults, the presence of synchronous pulmonary metastases. The role of chemotherapy in adult patients and the role of radiation therapy remain unclear. Even though negative margins are achieved, the majority of patients will have recurrence either locally or in the lungs.

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DISCUSSION

DR VICTOR F. TRASTEK (Rochester, MN): I enjoyed your presentation, Dr Perry, and congratulate you and your colleagues on providing information on a rare but difficult group of 14 patients, in particular those with recurrent or metastatic sarcoma to the chest wall. You have shown acceptable survival and no operative mortality after resection in this group.

We also continue to advocate aggressive resection for select patients with recurrent or metastatic disease to the chest wall but only if the primary disease is controlled, the disease is localized and can be completely resected, and the patient can tolerate the procedure. We still believe that rationale for such resection in this group remains controversial but we offer it to these patients because it is the best treatment option we have at this time for these particular patients.

Use of intraoperative frozen section analysis and current computed tomography and magnetic resonance scanning should provide margin-free resection of localized disease in most patients. Along these lines, I wonder if you could comment on including 9 patients with synchronous pulmonary metastases and 3 in whom the margins were positive after resection. Also, could you describe your current preoperative evaluation of both the primary and metastatic process, and how much free margin do you recommend in resections for patients with recurrent or metastatic disease?

A successful resection is also dependent on the ability to reconstruct the residual defect resulting in a healed wound. Full-thickness resection usually requires reconstruction of both the bony and soft tissue defect. In your series of 28 patients, 11 had bony reconstruction and only 2 were noted to have some type of soft tissue reconstruction. Although we agree that small bone defects (10 cm) in the skeletal wall do not have to be reconstructed, we do feel that most patients with defects larger than this will benefit from reconstruction to help stabilize the chest wall, provide coverage of thoracic structures, and provide a base for successful soft tissue reconstruction. We have had little morbidity using a prosthetic patch to accomplish this task in a clean wound. Along these lines, could you comment on the cause of wound complications in the 25% of patients in whom they developed?

DR PERRY: I certainly agree with Dr Trastek's comments regarding the appropriateness of excising recurrent or metastatic disease in a select group of patients only. I would emphasize that our indications are the same as his: the primary disease must be well controlled if it is a metastatic tumor, the lesion must appear to be resectable with negative margins, and the patient must be able to tolerate the procedure.

In terms of our preoperative staging protocol, I am sure it is similar to the type of staging that he does at the Mayo Clinic. We do a careful history and physical examination, and our staging procedures include computerized axial tomography or magnetic resonance imaging, or both.

In spite of that, much to our chagrin, there were many patients who had small metastatic deposits discovered at the time of operation. I do not know what else we could have done to prevent that from occurring with today's imaging technology.

In terms of what our wound complications were, seromas or a little bit of skin necrosis right at the margins of the wound were the most common complications that we saw. I do not know that there is anything that we could have done to prevent those, and I certainly do not think that additional reconstruction of the patients who did not get reconstruction would have prevented those complications.

We would disagree with his comments that most patients benefit from formal muscular reconstruction at the time of operation, as we have shown from our data that 38% of patients with large defects did quite well without formal bony reconstruction or muscle flaps. So we think that in select circumstances, depending on the experience and judgment of the surgeon, reconstruction is not always needed.

Ten-Year Experience With the Porcine Bioprosthetic Valve: Interrelationship of Valve Survival and Patient Survival in 1,050 Valve Replacements

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Robert A. Guyton, MD, Caryn L. Cohen, RN, Victor E. Corrigan, MD, and
Charles R. Hatcher, Jr, MD

Division of Cardiothoracic Surgery, Department of Surgery, and Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

The porcine bioprosthetic valve was used in 440 patients having isolated mitral valve replacement (MVR), 522 patients having isolated aortic valve replacement (AVR), and 88 patients having MVR + AVR between 1974 and 1981. Patients with associated surgical procedures were excluded. Mean follow-up was 8.3 years. At 10 years, there was no difference in patient survival between those having AVR and those having MVR. Reoperations were performed on 192 patients. Endocarditis was the reason for reoperation in 3.7% of patients who had MVR and 10.6% of those who had AVR. Structural valve degeneration was the reason for reoperation in 89.7% of MVR patients and 78.8% of AVR patients ($p = 0.04$). Hospital mortality among patients having valve reoperations was 4.7%. At 10 years, the freedom from valve reoperation for all causes and from structural valve degeneration was significantly better for the AVR group than the MVR group (74% ± 3% versus 61% ± 4%, $p = 0.004$; and 79% ± 3% versus 63% ± 4%, $p = 0.0006$, respectively). For patients in their 60s, the 10-year freedom from reoperation was 92% ± 2% for AVR and 80% ± 6% for MVR ($p =$ not significant). At 10 years, freedom from cardiac-related death and valve reoperation was best for both MVR and AVR patients in their 60s. Patients 70 years old or older rarely had reoperation but died before valve failure occurred. The 10-year freedom from all major valve-related events (cardiac-related death, reoperation, thromboembolism, endocarditis, and anticoagulant-related bleeding) was practically the same for both MVR and AVR patients (48% ± 3% versus 49% ± 3%, respectively). The porcine bioprosthetic valve is the valve of choice only for patients 60 years old or older. Patients in their 70s have an extremely low rate of reoperation but a high rate of cardiac-related death and do not outlive the prostheses.

(Ann Thorac Surg 1990;49:370–84)

The early and intermediate results of valve replacement using the porcine bioprosthetic valve (PBV) are now well known [1–4]. Although several studies [3, 5–8] have described the long-term prognosis after such replacement, these same large series often have several shortcomings: a short mean follow-up, inclusion of patients with associated medical conditions known to affect survival, and a population with a young mean age. The interrelationship between patient age and structural valve degeneration of the PBV has been emphasized [7, 9]. However, it is essential to examine this end point with a study that has a long follow-up and does not include patients with confounding medical problems.

The format of this study was developed to provide answers to questions relating to PBV usage that are asked frequently by both physicians and patients. Data from such an analysis should accurately state the chances of a given patient (1) being alive at the end of 10 years after isolated aortic valve replacement (AVR) or mitral valve replacement (MVR), (2) being free from valve reoperation during this period, and (3) being without the occurrence of any major valve-related morbid event, eg, cardiac-related death, reoperation (for whatever cause), thromboembolism, endocarditis, and anticoagulant-related bleeding necessitating hospitalization. Because patient age appears to have a pronounced effect on the answers to such questions, attempts have been made to interrelate age with both valve survival and patient survival.

In an effort to maintain a homogeneous patient population and produce a meaningful study representative of the long-term fate of patients undergoing isolated AVR or MVR, patients having associated cardiac procedures, patients in the pediatric age population, and patients having PBV implantation less than 5 years from the beginning of the follow-up were excluded.

Material and Methods

Between 1974 and 1981, the PBV was used almost exclusively for valve replacement at our institution. During this time, 1,050 patients underwent isolated MVR, isolated AVR, or AVR + MVR using either the Hancock or Carpentier-Edwards bioprosthesis. Excluded from the analysis was any patient having an associated cardiac procedure (eg, ascending aortic replacement, left ventric-

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ular aneurysm repair, or coronary revascularization). Eighty-eight of the 1,050 patients had combined AVR + MVR, and because of insufficient numbers for actuarial analysis, long-term results in these patients were not studied. Of the remaining 962 patients, 440 had isolated MVR and 522 had isolated AVR during the 7-year period. Ninety-two percent of the aortic prostheses and 91% of the mitral bioprostheses were Hancock valves; 8% and 9%, respectively, were Carpentier-Edwards valves.

Hospital or operative mortality included death from any cause within 30 days of the surgical procedure. Structural deterioration of a bioprosthetic valve was considered to be present with the occurrence of stenosis or regurgitation and included leaflet disruption, calcification, strut malfunction, or pannus entrapment of a leaflet. This diagnosis was made exclusively at the time of reoperation. Structural deterioration leading to death or disability without reoperation could not be documented. Excluded from the diagnosis of structural valve degeneration were those valves found at reoperation or autopsy to have thrombosis or infection, and valves that failed because of nonstructural dysfunction including paravalvular leak, patient–valve size mismatch, and trauma. Reasons for reoperation were determined by a detailed analysis of operative reports for 180 of the 192 patients having reoperation. For the remaining 12 patients, information was obtained by telephone from the physician, family, patient, or hospital.

Death and reoperation were considered the two most important major events that were reliably verified during follow-up. Consequently, they were expressed actuarially by age groups and for the total valve-replacement population. For purpose of analysis, age categories were arbitrarily divided into patients less than 40 years old and patients in their 40s, 50s, 60s, and 70s and older. This age grouping appeared useful clinically now that most surgeons avoid, whenever practical, using the bioprosthetic valve in patients in the first four decades of life. Analysis by age groups is important for more accurately predicting valve survival for any given patient.

Thromboembolism excluded causes due to infection but included any new permanent or transient focal or global neurological deficit and any peripheral arterial embolic episode after discharge from the hospital. Patients receiving aortic PBVs were not routinely anticoagulated. For patients with atrial fibrillation or left atrial thrombus who had MVR, a regimen of anticoagulation was begun shortly after operation.

Prosthetic valve endocarditis was based on positive blood cultures in the hospital or histological or bacteriological confirmation at reoperation, or both of these. It was confirmed by interviewing the patient or the family.

Follow-up was conducted by direct communication (telephone or letter) with the patient, family, attending physicians, or a combination of these. Additional information on patients who had died was obtained from the state bureau of records. Operative notes were reviewed for causes of reoperation. Follow-up was 99% complete; 11 patients were lost to follow-up.

Patient survival included operative mortality and was calculated by the method of Kaplan and Meier [10].

Table 1. Patient Demographics[a]

Variable	MVR	AVR	MVR + AVR	Total
No. of patients	440	522	88	1,050
% Male	144 (32.7)	360 (69.0)	36 (40.9)	540 (51.4)
Age (yr)				
Mean	53 ± 14	56 ± 15	48 ± 14	54 ± 15
Range	11–92	10–83	14–79	10–92

[a] Numbers in parentheses are percentages.

AVR = aortic valve replacement; MVR = mitral valve replacement.

Overall survival included death from cardiac-related and noncardiac causes. Cardiac-related deaths represented 75.5% of deaths from all causes (123/163) for AVR patients and 79.3% (119/150) for MVR patients. Survival free from thromboembolism, endocarditis, bleeding, valve reoperation, and valve reoperation for structural valve deterioration was also calculated by the method of Kaplan and Meier [10]. Significant differences of survival curves over time were calculated by the Mantel-Cox test [11] and of curves with early differences, by the method of Breslow [12]. All p values of less than 0.05 were considered significant. Major clinical events used to construct freedom curves were death, valve replacement, endocarditis, valve thrombosis or thromboembolism, and anticoagulant-related bleeding necessitating hospitalization. Age as a continuous variable was compared with valve survival using the Cox proportional hazards model [13].

Results

Mean follow-up of all patients was 8.3 years. Maximum follow-up was 13.1 years. Demographic data are presented in Table 1. Of the MVR patients, 33% were male, and of the AVR patients, 69%. Age ranged from 10 to 92 years (mean age, 54.0 ± 14.8 years; median age, 56 years).

Procedural characteristics, complications, and mortality are presented in Table 2. Hospital mortality during the period of entry into the study was 8.6% for isolated MVR and 4.8% for isolated AVR ($p = 0.017$). Sex of the patient did not significantly affect hospital mortality: 7.6% versus 9.1% for MVR and 5.0% versus 4.3% for AVR, male versus female patients (p = not significant).

Both isolated AVR and MVR were performed as an elective procedure in 96.6% of patients. Before the original operation, 55.3% of the MVR patients and 28.7% of the AVR patients were in New York Heart Association functional class III or IV.

Actuarial survival for patients undergoing isolated MVR and AVR is depicted in Figure 1. Patient survival curves have been separated into cardiac-related death and death from all causes. The rate of cardiac-related death was greatest in the first year and thereafter was relatively linear. At 10 years, there was no difference in patient survival (both cardiac-related and overall) between patients having AVR and those having MVR. An early difference (up to 8 years) reflects the higher hospital mortality after MVR compared with AVR.

Freedom from cardiac-related death is divided by age by decade in Figure 2. Survival was best for patients less

Table 2. In-Hospital Results[a]

Variable	MVR	AVR	MVR + AVR	Total	p Value
Emergent operation	15 (3.4)	20 (3.8)	1 (1.1)	36 (3.4)	NS
Valve size (mm)					
Mean	29 ± 2	24 ± 2	. . .	. . .	. . .
Range	19–35	15–33	. . .	. . .	. . .
Valve type					
Hancock	400 (90.9)	493 (94.4)	. . .	. . .	. . .
Carpentier-Edwards	40 (9.1)	29 (5.6)	. . .	. . .	. . .
Aortic cross-clamp time (min)	44 ± 19	74 ± 25	109 ± 32	. . .	<0.0001
IABP postop	23 (5.2)	18 (3.4)	7 (8.0)	48 (4.6)	0.12
Returned to OR (bleeding)	19 (4.3)	43 (8.2)	2 (2.3)	64 (6.1)	0.01
In-hospital CVA	27 (6.1)	16 (3.1)	8 (9.1)	51 (4.9)	0.01
Hospital deaths	38 (8.6)	25 (4.8)	8 (9.1)	71 (6.8)	0.04

[a] Numbers in parentheses are percentages.

AVR = aortic valve replacement; CVA = cerebrovascular accident (perioperative stroke); IABP = intraaortic balloon pump; MVR = mitral valve replacement; NS = not significant; OR = operating room.

than 50 years of age in both valve groups with no difference between AVR and MVR patients at 10 years. Freedom from cardiac-related death declined for both AVR and MVR patients in their 50s and 60s and, as expected, was lowest for patients 70 years old or greater. Only AVR patients in their 70s demonstrated a superior 10-year freedom from cardiac-related death compared with MVR patients of similar age (p = 0.046).

Reoperations were performed on 192 patients (85 AVR and 107 MVR patients), and 173 of these reoperations were during the 12-year period shown in the Figures. The mean age at reoperation was 53 ± 14 years for MVR patients and 49 ± 15 years for AVR patients (p = not significant). The mean interval between operations was 7.9 ± 3.0 years for MVR patients and 7.6 ± 3.1 years for AVR patients (p = not significant). Of the patients in this series, 24% (107/440) of those who underwent MVR and 16% (85/522) of those who underwent AVR have required valve reoperation. Reasons for reoperation are shown in Table 3. Endocarditis as a reason for reoperation occurred at almost three times the frequency for aortic bioprostheses as for mitral bioprostheses. Structural valve failure was a major problem with both bioprostheses but more so with the mitral valve. Hospital mortality for patients undergoing mitral or aortic valve reoperation was 4.7% (mitral, 5/107; aortic, 4/85).

Freedom from reoperation for all causes and freedom from structural valve degeneration at 10 years are illustrated in Figure 3. Note that at approximately the eighth year, there was an acceleration of the need for reoperation. Freedom from valve reoperation for all causes and freedom from reoperation for structural valve deterioration were significantly different between mitral and aortic valves (Table 4; see Fig 3).

Freedom from valve reoperation by age groups is depicted in Figure 4. Similarly, freedom from structural valve deterioration by age groups is seen in Figure 5. From these curves, it can be noted that valve reoperation for all causes and reoperation for structural valve degeneration decrease with advancing age. There were no reoperations in either the MVR or AVR patients in their 70s. The aortic bioprosthesis was superior to the mitral bioprosthesis in this regard except in patients 70 years old and older and patients less than 40 years of age. Aortic valve replacement patients in their 60s had a 10-year freedom from reoperation of 92% ± 2% compared with 80% ± 6% for MVR patients (p = not significant). The poorest performance with the lowest freedom from reoperation occurred in the MVR and AVR patients less than 40 years of age (47% ± 8% and 46% ± 7% at 10 years, respectively). The poor performance figure of 47% for MVR patients less than 40 years old was very similar to that of 48% ± 8% for MVR patients between 40 and 49 years of age. Valve survival was considerably better for patients in their 60s with intermediate results for patients in their 50s.

Actuarial freedom from both cardiac-related death and valve reoperation for MVR and AVR patients by age is shown in Figure 6. The best 10-year results for both valves occurred in the 60-year-old group (MVR, 57%; AVR,

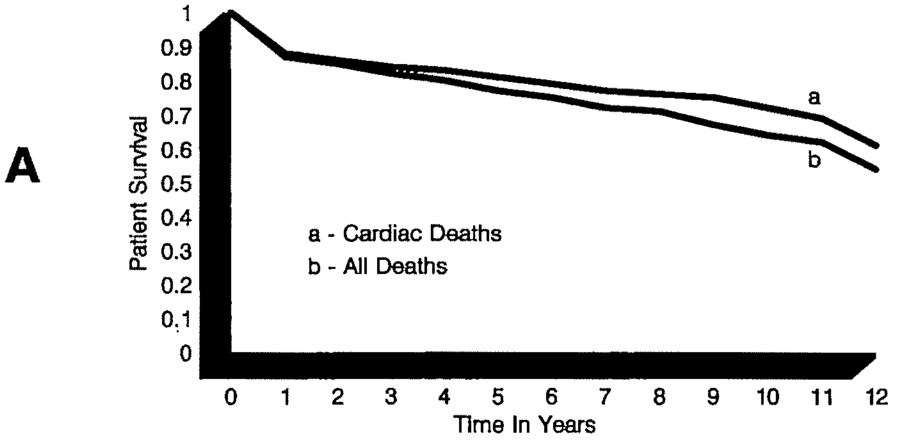
Table 3. Reason for Reoperation in 192 Patients Having Isolated Aortic or Mitral Valve Replacement[a]

Reason	MVR (n = 107)	AVR (n = 85)	p Valve
Endocarditis	4 (3.7)	9 (10.6)	0.06
Thrombosis or thromboembolism[b]	4 (3.7)	4 (4.7)	NS
Structural valve degeneration[c]	96 (89.7)	67 (78.8)	0.04
Nonstructural failure	3 (2.8)	5 (5.9)	NS
Paravalvular leak	2 (1.9)	3 (3.5)	. . .
Inappropriate sizing	1 (0.9)	1 (1.2)	. . .
Trauma	0	1 (1.2)	. . .

[a] Numbers in parentheses are percentages. [b] Thromboembolism means either cerebral or peripheral event after hospital dischage only; thrombosis refers to thrombotic malfunction of the valve. [c] This includes pannus ingrowth into valve leaflet.

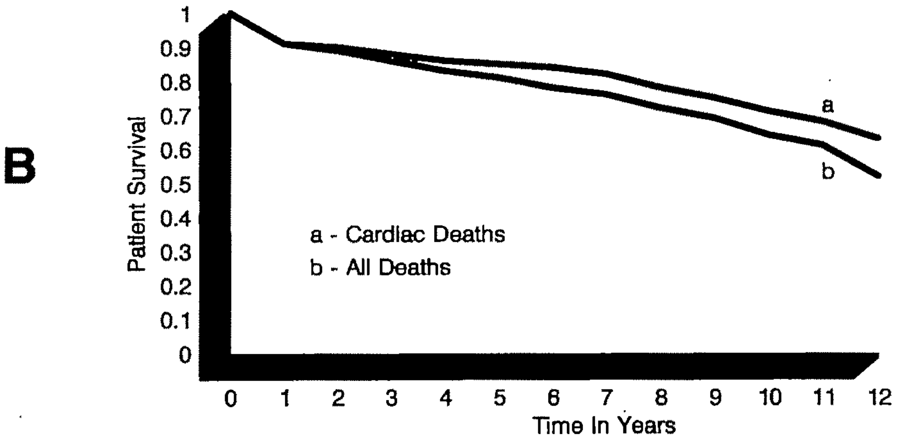
AVR = aortic valve replacement; MVR = mitral valve replacement; NS = not significant.

A



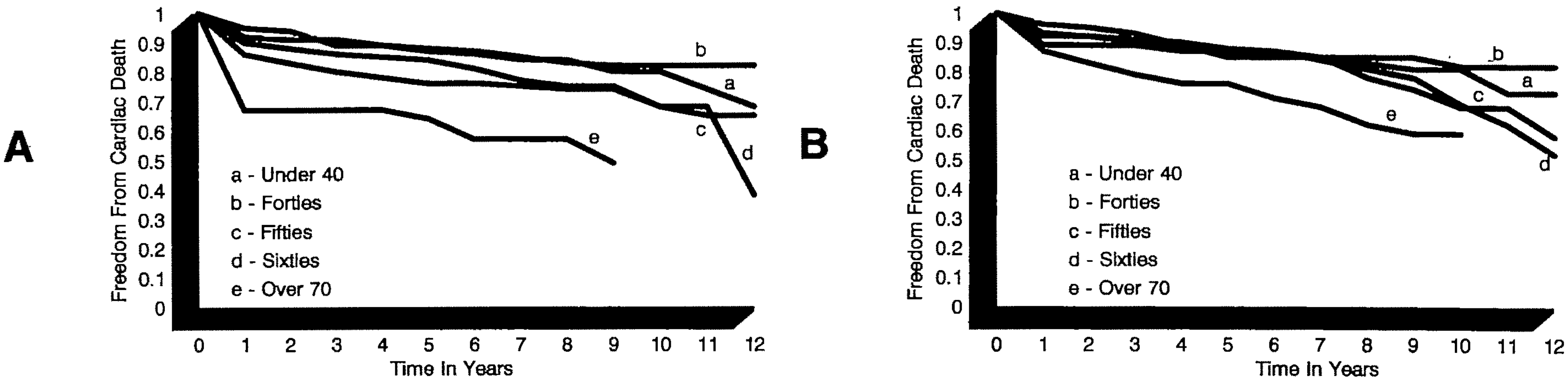
Cardiac Deaths													
n Remaining	440	375	361	344	330	316	289	246	206	144	103	70	39
Survival	1	.88	.86	.84	.83	.81	.79	.77	.76	.75	.72	.69	.61
n Dead	0	53	61	70	74	81	88	95	98	102	107	110	116
All Deaths													
n Remaining	440	375	361	344	330	316	289	246	206	144	103	70	39
Survival	1	.87	.85	.82	.80	.77	.75	.72	.71	.67	.64	.62	.54
n Dead	0	55	67	79	88	97	106	117	122	130	136	139	146

B



Cardiac Deaths													
n Remaining	522	465	448	426	407	388	344	293	215	160	112	69	32
Survival	1	.91	.90	.88	.86	.85	.84	.82	.78	.75	.71	.68	.63
n Dead	0	44	52	59	69	76	81	89	101	107	115	119	123
All Deaths													
n Remaining	522	465	448	426	407	388	344	293	215	160	112	69	32
Survival	1	.91	.89	.86	.83	.81	.78	.76	.72	.69	.64	.61	.52
n Dead	0	47	58	71	85	98	108	117	131	140	150	154	161

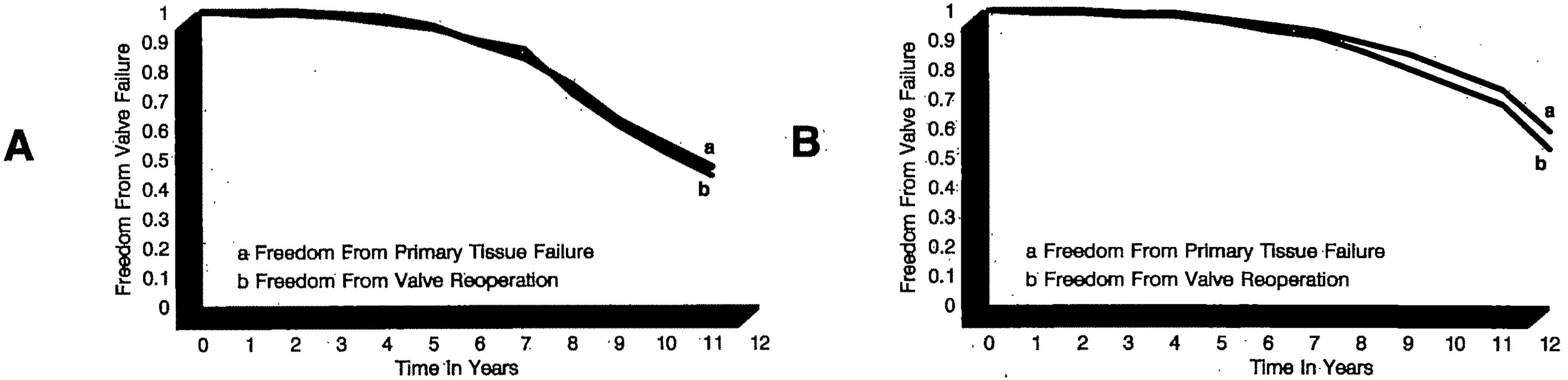
Fig 1. Survival free from cardiac-related death and overall actuarial survival of (A) patients having mitral valve replacement and (B) those having aortic valve replacement. Survival percentages for each year are noted in the tables below the curves.



Under 40													
n Remaining	76	64	62	59	57	55	53	48	43	35	29	17	11
Survival	1	.92	.91	.91	.89	.87	.86	.84	.84	.80	.80	.74	.68
n Dead	0	6	7	7	8	9	10	11	11	13	13	15	16
Forties													
n Remaining	78	71	68	64	63	62	59	53	47	36	25	21	12
Survival	1	.96	.94	.89	.89	.88	.87	.85	.83	.82	.82	.82	.82
n Dead	0	4	5	8	8	9	10	11	12	13	13	13	13
Fifties													
n Remaining	116	103	101	99	96	94	83	68	56	35	23	13	10
Survival	1	.90	.88	.86	.85	.84	.81	.77	.75	.75	.68	.65	.65
n Dead	0	12	14	16	17	19	22	26	27	27	30	31	31
Sixties													
n Remaining	131	111	104	96	90	85	78	66	50	33	23	16	5
Survival	1	.86	.83	.80	.78	.76	.76	.75	.74	.74	.68	.68	.38
n Dead	0	18	22	26	28	30	30	31	32	32	34	34	39
Over 70													
n Remaining	39	26	26	26	24	20	16	11	11	5			
Survival	1	.67	.67	.67	.67	.64	.57	.57	.57	.49			
n Dead	0	13	13	13	13	14	16	16	16	17			

Under 40													
n Remaining	81	71	69	66	65	63	60	56	42	35	29	17	7
Survival	1	.89	.89	.89	.87	.87	.86	.85	.83	.81	.81	.73	.73
n Dead	0	9	9	9	10	10	11	12	13	14	14	16	16
Forties													
n Remaining	76	72	71	69	66	60	57	52	42	33	25	14	8
Survival	1	.96	.95	.93	.89	.86	.85	.85	.85	.85	.82	.82	.82
n Dead	0	3	4	5	8	11	11	11	11	11	12	12	12
Fifties													
n Remaining	121	109	107	102	98	93	84	73	57	38	24	15	8
Survival	1	.92	.92	.90	.88	.87	.87	.85	.78	.74	.68	.68	.58
n Dead	0	9	10	12	14	15	15	17	23	25	28	28	30
Sixties													
n Remaining	145	130	125	121	116	111	97	77	53	41	24	18	8
Survival	1	.93	.92	.91	.90	.88	.87	.84	.81	.78	.69	.62	.52
n Dead	0	10	12	13	14	17	18	21	23	25	29	31	33
Over 70													
n Remaining	98	83	76	68	62	61	46	35	21	13	10		
Survival	1	.87	.83	.79	.76	.76	.71	.68	.62	.59	.59		
n Dead	0	13	17	20	23	23	26	28	31	32	32		

Fig 2. Actuarial freedom from cardiac-related death by age group for (A) mitral and (B) aortic valve replacement.



Freedom From Primary Tissue Failure													
n Remaining	440	370	363	331	309	285	250	202	160	107	68	43	24
FF Events	1	1	1	.99	.98	.95	.93	.89	.84	.75	.63	.55	.47
n Events	0	1	1	5	7	15	23	31	42	57	72	80	85
Freedom From Valve Reoperation													
n Remaining	440	370	353	331	309	285	250	202	160	107	68	43	24
FF Events	1	.99	.99	.98	.96	.94	.90	.87	.82	.72	.61	.52	.44
n Events	0	2	3	8	13	21	31	39	50	66	81	90	95

Freedom From Primary Tissue Failure													
n Remaining	522	464	447	419	395	366	312	255	183	127	86	50	20
FF Events	1	1	1	.99	.99	.97	.95	.93	.89	.85	.79	.73	.59
n Events	0	1	1	4	5	11	19	25	35	41	49	54	60
Freedom From Valve Reoperation													
n Remaining	522	464	447	419	395	366	312	255	183	127	86	50	20
FF Events	1	.99	.99	.98	.98	.96	.93	.91	.88	.80	.74	.68	.53
n Events	0	3	3	8	11	18	27	34	47	57	66	71	78

Fig 3. Freedom from (FF) valve failure depicting freedom from structural valve deterioration (primary tissue failure) and freedom from valve reoperation for all causes for (A) mitral and (B) aortic bioprostheses.

Table 4. Actuarial Freedom From Major Valve-Related Complications at 10 Years

10-Year Freedom From	MVR	AVR	*p* Value
Thrombosis and thromboembolism	0.93 ± 0.02	0.93 ± 0.02	NS
Endocarditis	0.96 ± 0.02	0.95 ± 0.01	NS
Anticoagulant-related bleeding	0.95 ± 0.02	0.98 ± 0.01	NS
Structural valve degeneration leading to reoperation	0.63 ± 0.04	0.79 ± 0.03	0.0006
Reoperation for all causes	0.61 ± 0.04	0.74 ± 0.03	0.004
Cardiac-related death	0.72 ± 0.03	0.71 ± 0.03	NS
Death from all causes	0.64 ± 0.03	0.64 ± 0.03	NS
Cardiac-related death or valve reoperation	0.53 ± 0.03	0.53 ± 0.03	NS
All valve-related events	0.48 ± 0.03	0.49 ± 0.03	NS

AVR = aortic valve replacement; MVR = mitral valve replacement; NS = not significant.

63%). The curves for elderly (≥70 years) patients were greatly influenced by death rather than reoperation, and therefore the freedom curves were not quite as good as those for the 60-year-old group. At the end of 10 years, only 40% of MVR and 38% of AVR patients less than 40 years of age had not died of cardiac-related causes or required reoperation. Mitral valve replacement patients in their 40s had a 10-year freedom from these two major events of only 39%.

Valve-related events after either AVR or MVR with a PBV are shown in Figure 7 and Table 4. At 10 years, the freedom from cardiac-related death, the freedom from cardiac-related death or reoperation, and the freedom from death from all causes, reoperation, thromboembolism, endocarditis, and anticoagulant-related bleeding were practically the same for both AVR and MVR patients. At the end of 10 years, slightly less than half of MVR and AVR patients were free from all major valve-related events. The actuarial 10-year freedom from valve thrombosis and thromboembolism, endocarditis, anticoagulant-related bleeding, structural valve degeneration leading to reoperation, and all valve-related events regardless of patient age for both AVR and MVR is shown in Table 4.

Age is naturally a continuous variable. Thus, age was examined as a correlate of valve survival using the Cox proportional hazards model [13]. The results of this analysis are shown in Figure 8. Valve survival by age is shown at 4, 6, 8, 10, and 12 years. For each group, there was improved valve survival with increasing age.

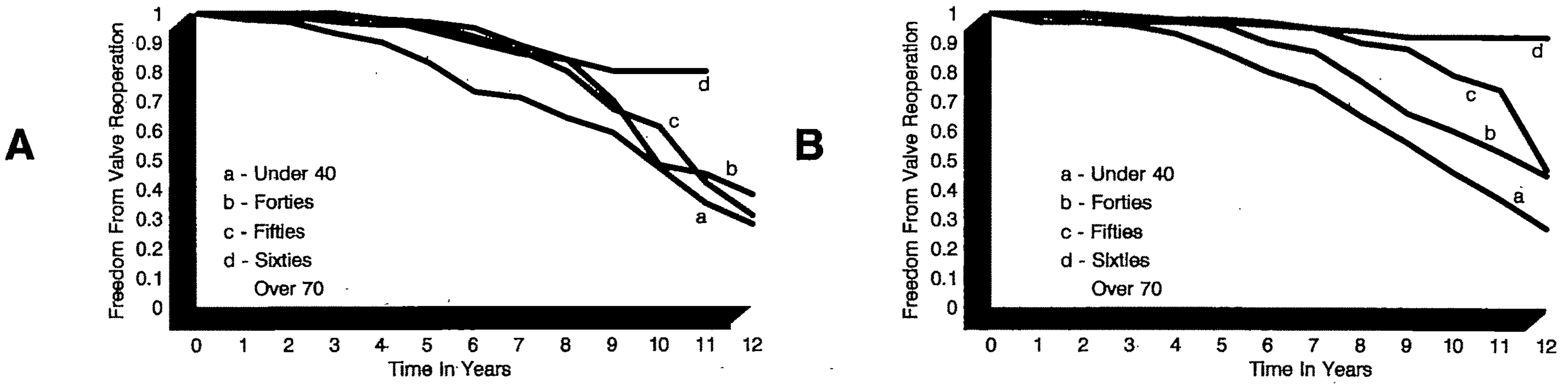
Comment

There are now considerable data concerning the prognosis for patients with PBVs after the first decade of implantation [1–9, 14, 15]. Methods of evaluation of both patient survival and valve survival have varied, but as of 1988, there are guidelines to standardize terms of reference for future valve evaluation [16]. Definitions of structural and nonstructural changes leading to valve reoperation have been carefully stated. As we have found in this study, problems still exist in regard to incidences of cardiac-related and noncardiac causes of death, valve-related deaths of any type, and valve-related death due to structural deterioration. In addition, the incidence of valve failure contributing to disability without death or reoperation is also unknown.

To permit uniform assessment of heart valve prostheses, the Stanford Group [17, 18] in 1977 proposed the term *overall valve dysfunction*, based on any valve-related complication—paravalvular leak, thrombosis or thromboembolism, endocarditis, prosthesis–patient size mismatch, structural degeneration—that resulted in reoperation or death. This concept was based on the patient's point of view. Our approach has been somewhat similar to the Stanford proposal and has attempted to answer in a useful actuarial format those questions most often asked by patients and physicians alike—namely, what are the chances 10 years after isolated AVR or MVR that a patient will (1) be alive, (2) need to have the valve replaced, (3) be living without valve reoperation, or (4) be living without valve reoperation and without endocarditis, thromboembolism, or anticoagulant-related bleeding necessitating hospitalization. It was obvious from the inception of the study that answers to some of these questions were age related, and decisions for matching the most appropriate valve with a given patient must take this factor into consideration.

Two characteristics intrinsic to the valve-replacement population can greatly affect the results of a given study. One is age of the patient, and the other is associated complex cardiac problems, eg, coronary artery disease, aortic and left ventricular aneurysm, or multiple-valve dysfunction. Because of the significant effect that associated diseases and complex operations exert on survival free from cardiac-related death and indirectly on valve survival, this study was carefully designed to include only patients having isolated valve replacement. Our mean age of 54 years for the entire series is consistent with that of many reported series [1, 9, 19, 20], but older than the patients discussed by others [3, 5–7]. Whereas we have excluded all patients having associated cardiac surgical procedures, others [1, 3, 5, 8] have included combined procedures in from 5% to 33% of the entire cohort. In an analysis of approximately 1,000 patients having valve replacement with a PBV, Zussa and co-workers [3] determined that the only significant risk factor for late death was an associated coronary artery bypass procedure performed at the time of the valve operation. Some [2] have thought the effect of associated coronary artery disease begins to influence survival after the sixth year of follow-up. Lytle and associates [9] also found that one of the major determinants of late survival was the presence of associated coronary artery disease. By exclusion of such patients, the present series can be used to determine the prognosis in patients having isolated PBV replacement.

The 10-year survival for patients having either isolated

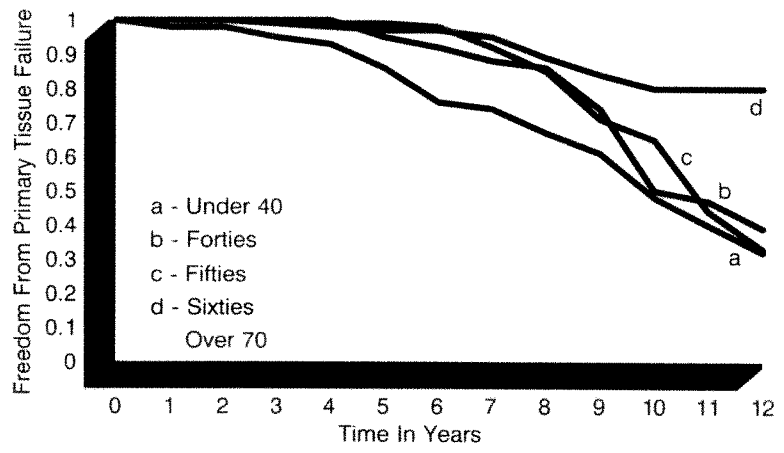


	0	1	2	3	4	5	6	7	8	9	10	11	12
Under 40													
n Remaining	76	63	60	55	51	45	38	33	27	21	13	5	3
Survival	1	.98	.97	.93	.90	.83	.73	.71	.64	.59	.47	.35	.28
n Dead	0	1	2	4	6	10	15	16	19	21	25	28	29
Forties													
n Remaining	78	70	66	63	61	57	52	45	40	28	16	13	10
Survival	1	1	1	1	.98	.94	.90	.86	.84	.70	.48	.45	.38
n Dead	0	0	0	0	1	4	6	8	9	15	23	24	26
Fifties													
n Remaining	116	101	98	94	90	88	75	57	43	27	19	9	5
Survival	1	.99	.99	.97	.96	.96	.92	.87	.80	.67	.61	.42	.31
n Dead	0	1	1	3	4	4	7	11	15	21	23	28	30
Sixties													
n Remaining	131	110	103	93	84	77	70	56	39	28	17	13	5
Survival	1	1	1	.99	.98	.97	.97	.95	.89	.84	.80	.80	.80
n Dead	0	0	0	1	2	3	3	4	7	9	10	10	10
Over 70													
n Remaining	39	28	28	26	23	18	15	11	11	5			
Survival	1	1	1	1	1	1	1	1	1	1			
n Dead	0	0	0	0	0	0	0	0	0	0			

	0	1	2	3	4	5	6	7	8	9	10	11	12
Under 40													
n Remaining	81	71	69	64	61	55	49	42	32	23	17	8	3
Survival	1	.97	.97	.96	.93	.87	.80	.75	.65	.56	.46	.37	.27
n Dead	0	2	2	3	5	9	13	16	21	25	29	32	33
Forties													
n Remaining	76	72	71	67	64	55	49	42	31	22	17	8	4
Survival	1.	1	1	.97	.97	.96	.90	.87	.77	.66	.60	.53	.45
n Dead	0	0	0	2	2	3	6	8	12	16	18	19	20
Fifties													
n Remaining	121	109	107	102	97	90	79	67	51	33	22	14	6
Survival	1	1	1	.99	.98	.97	.96	.95	.90	.88	.79	.74	.47
n Dead	0	0	0	1	2	3	4	5	8	9	12	13	17
Sixties													
n Remaining	145	129	124	119	113	107	91	72	49	37	21	15	6
Survival	1	.99	.99	.98	.98	.98	.97	.95	.94	.92	.92	.92	.92
n Dead	0	1	1	2	2	3	4	5	6	7	7	7	7
Over 70													
n Remaining	99	83	76	67	60	59	44	32	20	12	9		
Survival	1	1	1	1	1	1	1	1	1	1	1		
n Dead	0	0	0	0	0	0	0	0	0	0	0		

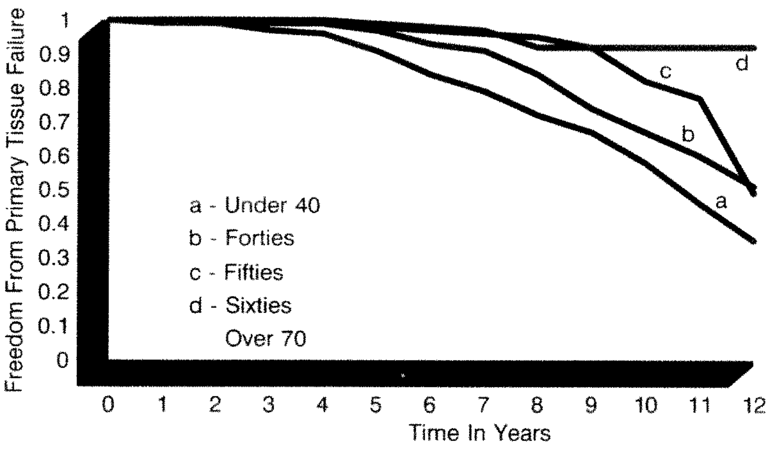
Fig 4. Freedom from valve reoperation by age groups for (A) mitral and (B) aortic valve replacement.

A



Under 40													
n Remaining	76	63	60	55	51	45	38	33	27	21	13	5	3
FF Events	1	.98	.98	.95	.93	.86	.76	.74	.67	.61	.48	.40	.32
n Events	0	1	1	3	4	8	13	14	17	19	23	25	26
Forties													
n Remaining	78	70	66	63	61	57	52	45	40	28	16	13	10
FF Events	1	1	1	1	1	.95	.92	.88	.86	.74	.50	.47	.39
n Events	0	0	0	0	0	3	5	7	8	13	21	22	24
Fifties													
n Remaining	116	101	98	94	90	88	75	57	43	27	19	9	5
FF Events	1	1	1	.99	.99	.99	.98	.92	.85	.71	.65	.44	.33
n Events	0	0	0	1	1	1	2	6	10	16	18	23	25
Sixties													
n Remaining	131	110	103	93	84	77	70	56	39	26	17	13	5
FF Events	1	1	1	.99	.98	.97	.97	.95	.89	.84	.80	.80	.80
n Events	0	0	0	1	2	3	3	4	7	9	10	10	10
Over 70													
n Remaining	39	26	26	26	23	18	15	11	11	5			
FF Events	1	1	1	1	1	1	1	1	1	1			
n Events	0	0	0	0	0	0	0	0	0	0			

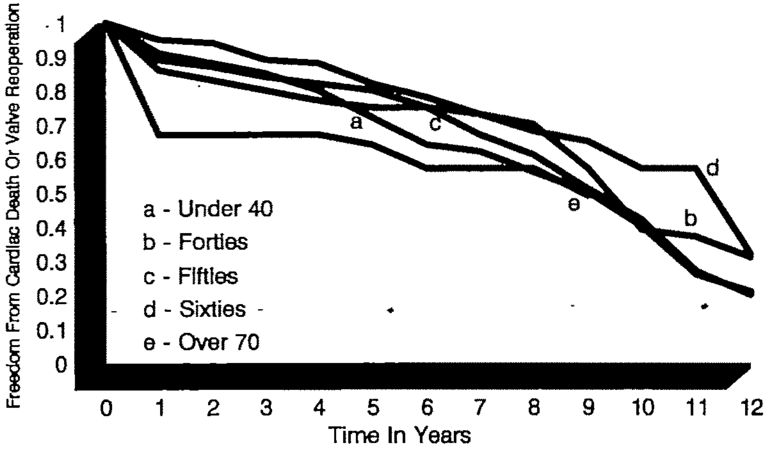
B



Under 40													
n Remaining	81	71	69	64	61	55	49	42	32	23	17	8	3
FF Events	1	.99	.99	.97	.96	.91	.84	.79	.72	.67	.58	.46	.35
n Events	0	1	1	2	3	6	10	13	16	18	21	24	25
Forties													
n Remaining	76	72	71	67	64	55	49	42	31	22	17	8	4
FF Events	1	1	1	.99	.99	.97	.93	.91	.84	.74	.67	.60	.51
n Events	0	0	0	1	1	2	4	5	8	11	13	14	15
Fifties													
n Remaining	121	109	107	102	97	90	79	67	51	33	22	14	6
FF Events	1	1	1	1	1	.99	.98	.97	.92	.92	.82	.77	.49
n Events	0	0	0	0	0	1	2	3	6	6	9	10	14
Sixties													
n Remaining	145	129	124	119	113	107	91	72	49	37	21	15	6
FF Events	1	1	1	.99	.99	.98	.97	.96	.95	.92	.92	.92	.92
n Events	0	0	0	1	1	2	3	4	5	6	6	6	6
Over 70													
n Remaining	99	83	76	67	60	59	44	32	20	12	9		
FF Events	1	1	1	1	1	1	1	1	1	1	1		
n Events	0	0	0	0	0	0	0	0	0	0	0		

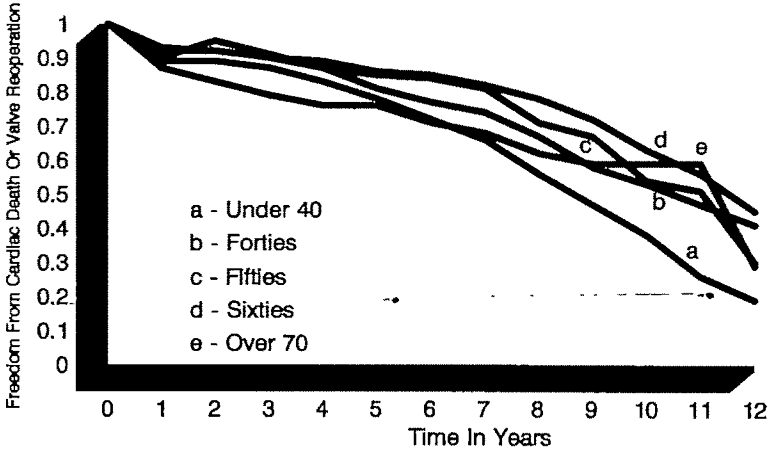
Fig 5. Freedom from (FF) structural valve deterioration (primary tissue failure) by age groups for (A) mitral and (B) aortic bioprostheses.

A



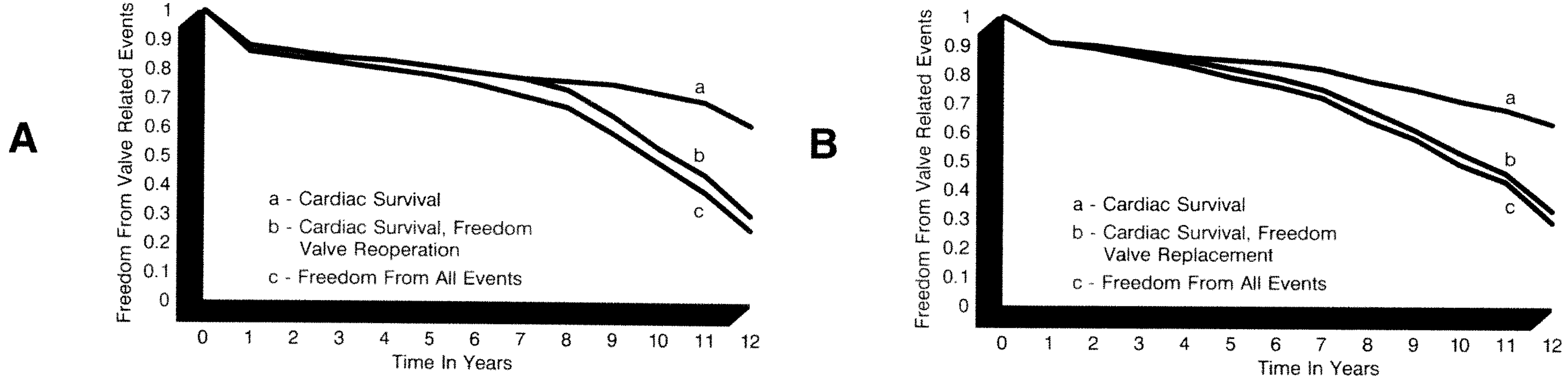
Under 40													
n Remaining	76	63	60	55	51	45	39	35	28	22	15	5	4
FF Events	1	.91	.88	.85	.80	.72	.64	.62	.56	.50	.40	.26	.21
n Events	0	7	9	11	14	19	24	25	28	31	35	40	41
Forties													
n Remaining	78	71	68	64	62	58	53	46	41	29	16	14	10
FF Events	1	.95	.94	.89	.88	.82	.78	.73	.70	.57	.39	.37	.31
n Events	0	4	5	8	9	13	16	19	21	28	36	37	39
Fifties													
n Remaining	116	102	100	96	92	90	76	58	44	27	19	9	5
FF Events	1	.89	.87	.84	.82	.80	.75	.67	.61	.51	.42	.27	.20
n Events	0	13	15	19	21	23	29	36	41	47	51	57	59
Sixties													
n Remaining	131	111	104	96	89	83	76	64	47	29	21	16	5
FF Events	1	.86	.83	.80	.77	.75	.75	.73	.68	.65	.57	.57	.32
n Events	0	18	22	26	29	32	32	33	37	39	42	42	47
Over 70													
n Remaining	39	26	26	26	24	20	16	11	11	5			
FF Events	1	.67	.67	.67	.67	.64	.57	.57	.57	.49			
n Events	0	13	13	13	13	14	16	16	16	17			

B



Under 40													
n Remaining	81	71	69	65	62	56	50	43	32	23	17	9	3
FF Events	1	.89	.89	.87	.83	.78	.72	.66	.56	.47	.38	.26	.19
n Events	0	9	9	10	13	17	21	25	31	36	40	45	46
Forties													
n Remaining	76	72	71	67	64	57	51	44	35	25	18	9	6
FF Events	1	.96	.95	.91	.87	.81	.77	.74	.67	.58	.53	.47	.41
n Events	0	3	4	7	10	14	17	19	23	27	29	30	31
Fifties													
n Remaining	121	109	107	102	97	91	81	69	52	36	22	14	6
FF Events	1	.92	.92	.90	.87	.85	.84	.81	.71	.67	.54	.51	.30
n Events	0	9	10	12	15	17	18	21	29	32	38	39	44
Sixties													
n Remaining	145	130	125	120	115	109	94	75	50	38	21	15	6
FF Events	1	.93	.92	.90	.89	.86	.85	.82	.78	.72	.63	.58	.45
n Events	0	10	12	14	16	19	21	24	27	30	34	36	38
Over 70													
n Remaining	99	63	76	68	62	61	46	35	21	13	10	5	1
FF Events	1	.87	.83	.79	.76	.76	.71	.68	.62	.59	.58	.58	.29
n Events	0	13	17	20	23	23	26	28	31	32	32	32	33

Fig 6. Freedom from (FF) cardiac-related death and valve reoperation by age groups for (A) mitral and (B) aortic valve replacement.



Cardiac Survival													
n Remaining	440	375	361	344	330	316	289	246	206	144	103	70	39
FF Events	1	.88	.86	.84	.83	.81	.79	.77	.76	.75	.72	.69	.61
n Events	0	53	61	70	74	81	88	95	98	102	107	110	116
Survival, Freedom Valve Reoperation													
n Remaining	440	375	361	344	330	316	289	246	206	144	103	70	39
FF Events	1	.88	.86	.84	.83	.81	.79	.77	.73	.64	.53	.44	.30
n Events	0	53	61	70	74	81	88	97	108	130	152	170	189
Freedom From All Events													
n Remaining	440	368	353	335	319	302	273	229	191	131	94	62	32
FF Events	1	.86	.84	.82	.80	.78	.75	.71	.67	.58	.48	.38	.25
n Events	0	60	69	79	85	95	106	118	130	155	176	194	212

Cardiac Survival													
n Remaining	522	465	448	426	407	388	344	293	215	160	112	69	32
FF Events	1	.91	.90	.88	.86	.85	.84	.82	.78	.75	.71	.68	.63
n Events	0	44	52	59	69	76	81	89	101	107	115	119	123
Survival, Valve Replacement													
n Remaining	522	465	448	422	400	374	322	266	190	135	88	52	22
FF Events	1	.91	.90	.88	.85	.82	.79	.75	.68	.61	.53	.46	.33
n Events	0	44	52	63	76	90	103	117	141	157	173	182	192
Freedom From All Events													
n Remaining	522	463	444	416	391	363	311	254	183	129	86	51	21
FF Events	1	.91	.89	.86	.83	.79	.76	.72	.64	.58	.49	.43	.29
n Events	0	46	56	70	86	102	116	133	158	174	191	200	211

Fig 7. Freedom from (FF) all valve-related events for (A) mitral and (B) aortic valve replacement patients. Events include cardiac-related death, reoperation, thromboembolism, endocarditis, and anticoagulant-related bleeding necessitating hospitalization.

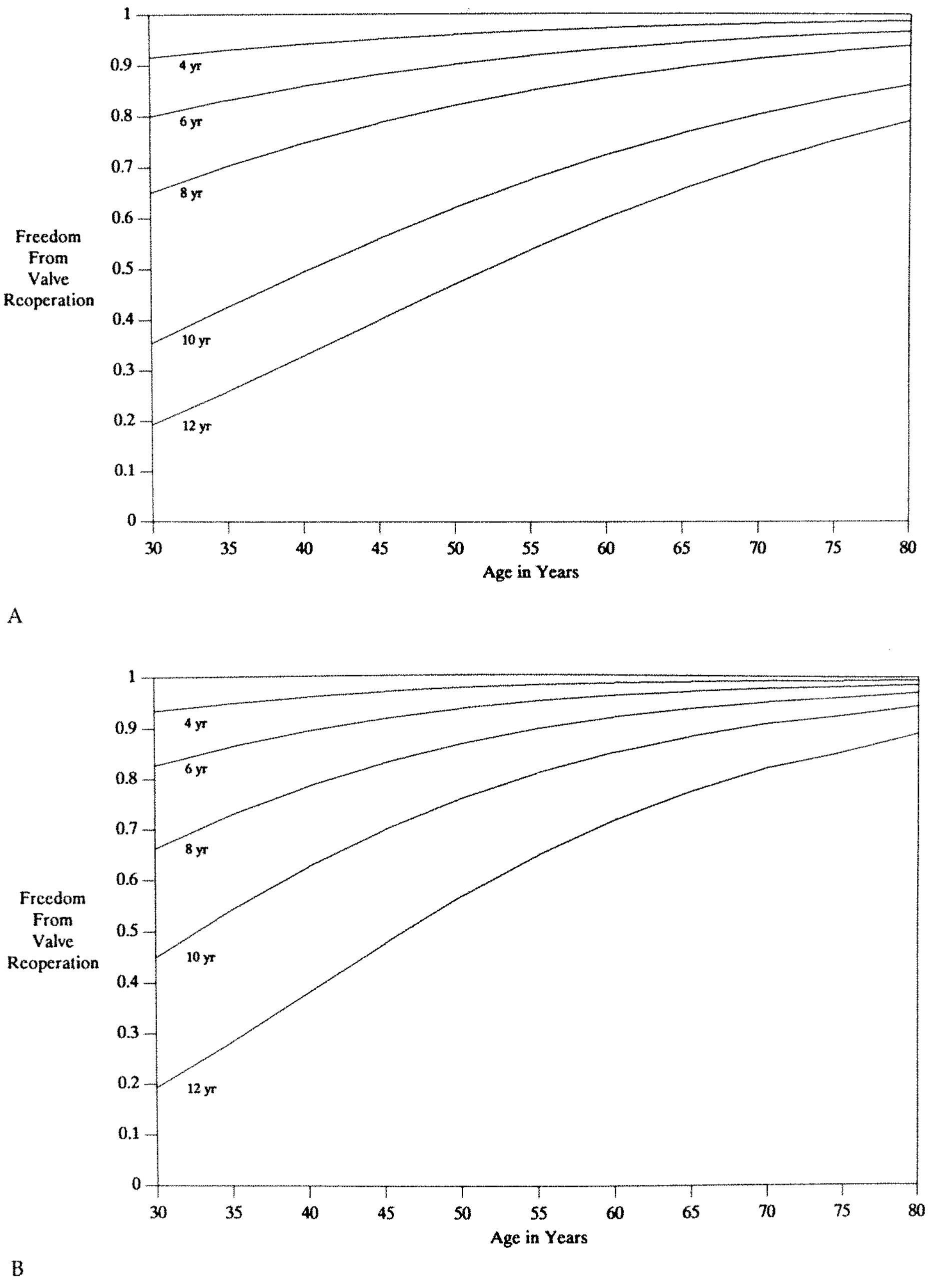


Fig 8. Cox proportional hazards model to evaluate freedom from valve reoperation by age at 4, 6, 8, 10, and 12 years after (A) mitral and (B) aortic valve replacements.

AVR or MVR was 64%, slightly less than that of Gallucci and colleagues [15] (70% with a slightly lower mean population age of 47 years), approximately the same as that of Lytle and co-workers [9], and slightly better than that recently reported by Magilligan and coauthors [14]. The better overall survival of patients having AVR with a bioprosthetic valve compared with those having MVR with a bioprosthetic valve up to the eighth year can be explained by the higher initial early mortality in the latter group. As expected 10-year survival free from cardiac-related death was best for patients in their 40s having either AVR or MVR. Surprisingly, patients younger than 40 years did less well, and this may have been a consequence of more complex coexisting congenital heart disease. There was a difference in survival free from cardiac-related death between AVR and MVR patients only in those 70 years old or older, but close inspection of the actuarial curves reveals that the difference at 10 years of 59% and at 9 years of 49%, respectively, was related to the higher hospital mortality of elderly MVR patients. Lytle and associates [9] have recently shown age to be the most profound determinant of in-hospital mortality among patients having AVR, and its most apparent influence was in patients 70 years old or older.

Overall patient survival is only partially helpful in interrelating the most appropriate valve for a given patient. By separating survival free from cardiac-related death from overall patient survival, it has been shown that differences in survival at 10 years for the former category between bioprosthetic and mechanical valves were significantly more profound than when all causes of death were considered [9]. However, difficulties can arise in excluding some patients when constructing curves for survival free from cardiac-related death. Patient deaths excluded because of trauma (automobile accidents can be secondary to embolic or arrhythmic events or sudden valve disruption) can lead to erroneous analysis. However, by eliminating all noncardiac causes of death, a more homogeneous cohort of patients is available for study, and presumably the results will be more meaningful clinically. In this study we have presented both.

Reoperation for whatever reason was performed at a relatively young age (mean age, 53 years for MVR and 49 years for AVR patients), and this in part explains the low reoperative hospital mortality at our institution. Other reasons probably relate to the initial exclusion of patients with multiple-valve disease and patients with associated cardiac conditions. Reported reoperative mortality has ranged from 5.6% to 16% [1, 6, 7, 9, 21] for aortic and 11% to 13% for mitral valve reoperations [6, 7, 17, 21]. Magilligan and colleagues [14] noted that the primary risk factors affecting reoperative mortality in their series were emergency procedure and preoperative New York Heart Association class IV status.

Endocarditis and thromboembolism in our series, as in others [1, 11, 14, 19, 20], occurred rather infrequently as demonstrated by the actuarial 10-year freedom from each complication. This is in agreement with the findings of Magilligan and co-workers [14] (combined valve freedom from thromboembolism, 92%; freedom from endocarditis, 93%) and Cobanoglu and associates [19] (thromboembolism after AVR, 95%; MVR, 90%). Some investigators [14] have shown that the risk of thromboembolism is high in the first several years and then lower, but continuous, thereafter. Others [9] have demonstrated that the rate is constant throughout the follow-up period. In our series, nonstructural failure (inappropriate valve size or paravalvular leak) was twice as common in AVR patients as MVR patients as a reason for reoperation, and this was due primarily to paravalvular leak. Whereas endocarditis as a reason for reoperation was seen much more frequently with AVR patients (almost three times more common than with MVR patients), thrombosis or thromboembolism surprisingly occurred with almost the same frequency in the two valve replacement groups. The primary reason for reoperation regardless of valve location in our series was structural valve degeneration, and this was the case in approximately 79% of AVR patients and 90% of MVR patients.

This study demonstrates that freedom from valve reoperation for whatever cause is significantly better at 10 years after AVR than MVR (74% versus 61%; $p = 0.004$). Interestingly, our freedom from reoperation at 10 years agrees closely with that of Cobanoglu and colleagues [19] for freedom from all causes of Hancock aortic or mitral valve failure (defined as any valve-related complication, eg, infection, embolus, bleeding, thrombosis, or leak causing death or necessitating reoperation). It also agrees with the recent study by Perier and co-workers [22] from the Hôpital Broussais on the 10-year evaluation of the mitral PBV, in which the freedom from structural valve deterioration was 65% and the freedom from reoperation was 64%. Our findings are also in agreement with those of Jamieson [7], Schoen [23], and their colleagues, who have documented the superior performance (less structural valve degeneration) of the Carpentier-Edwards PBV in the aortic position compared with the same valve in the mitral position.

In our study, the superior freedom from reoperation with aortic bioprostheses compared with mitral bioprostheses correlated closely with the superior freedom from structural valve deterioration of the aortic valve at 10 years (79% versus 63%; $p = 0.0006$). It can be speculated that the reason for the superior performance of the porcine bioprosthesis in the aortic position compared with that in the mitral position is the exposure of the former to lower diastolic pressure and the latter to the much higher pressure of ventricular systole at the time of valve closure. Magilligan and colleagues [8], however, found no difference in freedom from structural degeneration between the aortic or mitral bioprosthesis at 5 or 10 years. The data of Jamieson [7], Perier [22], and their associates on the incidence of structural valve degeneration with the Carpentier-Edwards valve were similar to those with the Hancock bioprosthetic valve. Spencer and co-workers [2] also found no significant difference in survival free from cardiac-related death between the two types of tissue prosthesis.

Interestingly, Jamieson and associates [7] found the risk of structural valve failure to be the same for aortic and mitral prostheses in the intermediate age group (30 to 59 years), but in their older patients (≥60 years), the performance of the aortic prosthesis was superior to that of the mitral prosthesis. In our study, both the freedom from structural valve failure and the freedom from reoperation for all causes were continuously age related for both prostheses and were always better as the ages of the patients increased. The aortic prosthesis outperformed the mitral prosthesis in all age groups except the very old (≥70 years) and very young (<40 years). The reason for the difference between the finding of Jamieson and co-workers [7] that the aortic prosthesis was not superior to the mitral prosthesis in the intermediate age groups and our own finding is not apparent but may be related to both use of different age categories and possibly fewer numbers of patients followed between the crucial eighth and tenth years when structural valve degeneration accelerates. Analysis of freedom from reoperation or structural valve degeneration by age demonstrated that very few patients having either AVR or MVR in their 70s will ever require reoperation for structural valve deterioration or other causes. Further, at the end of 10 years, approximately 92% of aortic and 80% of mitral bioprostheses will not have been replaced in the 60-year-old group of patients. Extremes of age negate the advantage of the aortic bioprosthesis over the mitral, and in both valve groups, patients less than 40 years of age had a freedom from reoperation at the tenth year of less than 50%.

In examining for freedom from the two most serious events associated with valve replacement, cardiac-related death and reoperation, the best results were obtained in patients 60 to 69 years old or older, and this was true for both aortic and mitral bioprostheses. These data confirm that cardiac-related death was the limiting factor in a favorable long-term result in patients more than 70 years of age. There was an almost complete freedom from reoperation in the 70-year-old group of AVR and MVR patients, and only an 8% 10-year incidence of reoperation in the 60- to 69-year-old AVR patients. This is perhaps the strongest argument for restricting use of the porcine bioprosthesis to patients 60 years old or older unless there are contraindications to the use of mechanical devices, eg, female patients desiring pregnancy, patients who do not comply with the anticoagulation regimen, and patients who desire no anticoagulation and are willing to undergo a future reoperation [5, 7, 14].

The present study demonstrates on an actuarial basis that for patients of all ages, 26% of aortic and 39% of mitral bioprostheses will have been replaced by the tenth year. In addition, when considering all major valve-related events for adults of all ages, AVR and MVR patients behave similarly and the following holds true at the end of 10 years: 64% are alive, 53% are free from cardiac-related death and reoperation, and approximately 49% are free from cardiac-related death, reoperation, thromboembolism, and endocarditis. This event-free survival was similar to the event-free survival at 10 years of 43% reported by Lytle and associates [9] for Hancock and Carpentier-Edwards aortic bioprostheses. In our study, freedom from both cardiac-related death and reoperation at 10 years was best for patients in their 60s. This group is served best by use of the PBV. Increased late mortality (cardiac-related and noncardiac) and past reluctance to recommend reoperation for older patients (≥70 years) both serve to explain the enhanced freedom from reoperation in the very elderly patient group. We reiterate that valve survival is continuously related to age, as demonstrated in Figure 8.

We conclude from this study that freedom from both reoperation and death and freedom from all events might be a more meaningful way to evaluate the patient–valve interrelationship. Valve survival alone in older patients can be misleading because older patients die before the expected time of structural degeneration. In patients 70 years old or older, the PBV lasts the life of the patient, and it is the valve of choice for the elderly.

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DISCUSSION

DR W. R. ERIC JAMIESON (Vancouver, BC, Canada): Dr Jones and colleagues have performed an extensive evaluation of their porcine bioprosthetic experience in the determination of overall freedom of death, freedom from valve-related reoperation, and overall freedom from cardiac-related death, reoperation, and standard valve-related complications. It has been a distinct privilege to review their documentation and now to discuss their findings.

The population base comprises over 1,000 patients implanted with isolated aortic and mitral prostheses, with the standard Hancock porcine bioprosthesis used in 90% of their patients.

Jones and associates have identified two distinguishing features between the performance of MVR and AVR, namely, structural valve deterioration and reoperation for all causes. The freedom from structural valve deterioration for mitral valve replacement was 63% and for aortic valve replacement, 79%.

At the University of British Columbia, in a population in whom the standard Carpentier-Edwards prosthesis was implanted in both isolated and concomitant procedures, the freedom from structural valve deterioration was 72% compared with their 63% for MVR and 83% compared with 79% for AVR. This slightly better freedom from structural valve deterioration probably can be explained by the mean age of our population, which is slightly older, and our freedom from reoperation parallels that for structural valve deterioration as it does in the series of Jones and associates. Jones and associates have illustrated the advanced failure of porcine prostheses in MVR patients younger than 60 years and AVR patients younger than 50 years.

Jones and associates consider the modality of overall cardiac-related death. Our question to them is, what is their freedom from valve-related mortality related to the prosthesis? Our freedom from valve-related mortality was 90%, and it is our concern that in this patient population, who presumably did not have ischemic heart disease, the freedom from cardiac-related death is exceedingly high. The inclusion of all cardiac-related deaths in an overall composite assessment does not truly reflect valve performance.

Dr Jones, can you elaborate on this aspect of your assessment and inform us of the specific valve-related mortality?

DR LAWRENCE H. COHN (Boston, MA): Dr Jones and associates have presented some very excellent data, conforming to the new guidelines set up by the Liaison Committee of The Society of Thoracic Surgeons and the American Association for Thoracic Surgery on valve reporting guidelines. These are quite solid 10-year data on primary MVR and AVR with a PBV.

My colleagues and I recently presented our 15-year data on the Hancock porcine valve at the meeting of the American Surgical Association and have similar but slightly differing results. For example, structural degeneration of the mitral valve at 10 years showed decreasing freedom from this morbid event at the 15-year mark. This amounts to a freedom from structural valve degeneration at about 10 years of about 78%, which is somewhat better than what Jones and associates have presented.

Why is this? The reason, I think, is one of the factors that was mentioned by Dr Jamieson, which is that we included all patients with all different types of operations, particularly coronary bypass—and in our group, about 30% of the patients had concomitant coronary bypass. Also, the mean age of our patients was higher, 60 years as opposed to 53 years in the study by Jones and associates.

I am using this to point out the fact that all these other factors are very important when you look at the analytical data on any kind of operation for cardiac surgery, and I think that the reason that morbidity rates differ is that in many series patients die before the valve wears out.

Gary Grunkemeier, the biostatistician who has worked with Dr Albert Starr in Oregon for a long time, independently came to the same conclusion. He analyzed a tremendous amount of porcine valve data in the literature and concluded that the potential failure of the porcine valves should be higher than is actually reported, but patient survival modifies this curve so that the percent free area is actually quite a bit less depending on the frequency of preoperative morbid factors in the patient population. Jones and associates have done a great service showing us the pure unadulterated risk factor group in evaluating this particular valve by excluding all other operative procedures.

Dr Jones, could you comment on your impressions of what I have just stated and also tell us why you think mitral valves degenerate faster than the aortic valves and, conversely, why aortic valves become infected more frequently than mitral valves?

DR L. HENRY EDMUNDS, JR (Philadelphia, PA): This analysis is patient oriented. It provides the when and how likely data regarding the patient's greatest concerns of death, reoperation, and serious complications. Thromboembolism and valve-related complications are uncommon in this series, so in closing perhaps Dr Jones will comment on the use of anticoagulants and platelet inhibitors in these patients.

This analysis also refers to a relatively homogeneous subset of patients. Although patients with a combination of ischemic and valvular heart disease would like to know what is in store for them, this paper separates the two groups and provides important information about the patients without associated cardiac diseases.

Last, Dr Jones and his colleagues have provided us age-stratified data that clearly show that age at operation predicts different futures. This gives them a solid data base for recommending the bioprosthesis for older patients and, by inference, a mechanical prosthesis for younger ones.

Now, with all this praise, perhaps one gentle criticism is worth a mention. Like many of us, Jones and associates used a 30-day operative mortality. However, with modern antibiotics, intravenous feeding, ventilators, dialysis machines, new inotropes, and artificial assist devices, any competent cardiac surgeon can keep a critically ill patient alive for 30 days. I do not think this achievement is necessarily in the patient's best interest.

DR JONES: Dr Jamieson deserves a great deal of credit for being the first to demonstrate in a very large series that there was a difference in the durability of the mitral and aortic bioprosthesis and was the first to stratify patients by age groups and make predictions of valve and patient survival. We hope that we have carried this initial idea a little bit further, giving some baseline data for a very homogeneous group without associated diseases or surgical procedures.

The freedom from valve-related mortality is an extremely good one. When patients die, they frequently die with little information available. The only clean data are whether they are alive or dead. Cause of death can be extremely difficult to ascertain. We have chosen to present an analysis of freedom from cardiac-related death as well as freedom from death (all causes), reoperation, and serious valve-related morbidity as the most meaningful format to evaluate overall valve function.

Dr Cohn has mentioned the very important aspect of including coronary bypass patients with valve replacement patients, which changes the curves and the expectation of survival, and he has asked why there is a difference in degeneration. We have always presumed the accelerated degeneration of the mitral over the aortic prosthesis was caused by the exposure of the mitral leaflets to high systolic pressure versus the lower diastolic pressure with the prosthesis in the aortic position.

Dr Edmunds in his usual fashion has praised and then cleverly criticized the presentation. Only MVR patients having giant left atrium, atrial fibrillation, or atrial thrombus are anticoagulated. Patients having valve replacement with the bioprosthesis are not anticoagulated. I think the answer to his question about low rate of thromboembolism and the difference in the 10-year freedom from thromboembolism in this group is related to the fact that coronary bypass patients or patients with coronary disease were excluded.

Rejection and Infection After Pediatric Cardiac Transplantation

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Cardiac transplantation has only recently become an accepted therapeutic modality for children and adolescents with end-stage cardiomyopathy. Long-term survival, the incidence of rejection, and the incidence of infection are still being defined. From 1985 to 1989, 21 children aged 6 months to 19 years (average age, 11.2 years) underwent cardiac transplantation at our institutions. Eighteen survived the operative period and have been followed for 5 to 49 months (average follow-up, 24 months). All operative survivors have received triple-drug immunosuppression consisting of cyclosporine, azathioprine, and prednisone. During follow-up, 7 patients have been treated on 12 occasions for rejection as documented by endomyocardial biopsy. Eight (67%) of the 12 episodes of rejection occurred in the presence of subtherapeutic cyclosporine levels. Two of the 7 patients treated for rejection have subsequently died of ongoing cardiac rejection and arrhythmia. There have been no perioperative or late deaths from infection. Bacterial sepsis was identified and treated twice during follow-up, viral infections on five occasions, and fungal infection once. Actuarial 1-year survival and 3-year survival of the 18 operative survivors are 94% and 78%, respectively. In the first 7 months after cardiac transplantation, 73% of patients were free from rejection and 83% were free from serious bloodborne infection. We conclude that (1) the incidence of rejection and infection is low with triple-drug immunosuppression; (2) rejection episodes occur most commonly within the first year after cardiac transplantation but can occur late; (3) rejection can often be associated with subtherapeutic cyclosporine levels; (4) major bacterial infection can occur in association with a common disease process but appears to respond to standard antibiotic therapy; and (5) viral infections have been well tolerated by the patients.

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Orthotopic cardiac transplantation has become accepted treatment of end-stage cardiomyopathy in adults in whom all medical and surgical therapy has been exhausted. The addition of cyclosporine to the posttransplantation immunosuppression regimen has dramatically decreased episodes of rejection as well as infection and has improved both the length and quality of life of adult patients after transplantation [1]. Patients who have undergone cardiac transplantation at our institutions since December 1983 are treated postoperatively with low-dose cyclosporine, azathioprine, and prednisone. Our group [2] has reported an actuarial 1-year survival rate of 94% (actuarial 3-year survival rate, 90%) after orthotopic cardiac transplantation in adult patients treated by this protocol. Eighty-eight percent of survivors are rejection free at 1 year [3], and the incidence of serious infection has been markedly reduced [3]. Nearly all of the survivors have returned to an active life and have no cardiac symptoms.

Until recently, cardiac transplantation in childhood has been a relatively uncommon procedure. The reported actuarial 1-year survival rate has been lower in children (64%) than adults [4]. The use of cyclosporine as well as better recipient selection has improved the recently published 1-year survival rate for children to 83%, which favorably approaches that of adults [5]. Few institutions have extensiveexperience with cardiac transplantation in childhood [6–10], and often within a series, more than one immunosuppression protocol has been employed [7] and more complex transplantation procedures (eg, combined heart-liver) [7] or patient groups [8, 9] are included, thus making interpretation of the results difficult. In some reports [8, 9], rejection has been diagnosed by noninvasive methods, which can overestimate its actual occurrence. The experience reported indicates, however, that acute rejection has occurred in the majority of long-term survivors [6–9] and that infectious complications are common and can be lethal [6, 11].

Within a 3½-year period at our institutions, 18 of 21 children ranging in age from 6 months to 19 years who underwent heart transplantation survived to hospital discharge. All 18 long-term survivors have been immunosuppressed postoperatively with low-dose cyclosporine, azathioprine, and prednisone. Our review of the incidences of rejection and infection in children receiving this combination of immunosuppressive agents after cardiac transplantation forms the basis of this report.

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Table 1. Preoperative Hemodynamics

			Preoperative Hemodynamics					
Patient No.	Sex	Age (yr)	Cardiac Index (L/min/m^2)	Mean Pulmonary Artery Pressure (mm Hg)	Pulmonary Artery Occlusive Pressure (mm Hg)	Indexed Pulmonary Vascular Resistance (Wood units [m^2])	Conditions	Operative Outcome
1	M	15.3	4.5	20	11	2.0	Nitroprusside	Alive
2	M	15.2	1.9	40	35	1.7	Nitroprusside, dobutamine, O_2	Alive
3	M	15.5	4.0	35	20	3.8	Nitroprusside	Alive
4	M	0.5	2.7	24	14	3.7	Room air	Alive
5	F	14.8	2.7	34	25	3.3	Room air	Alive
6	M	16.2	1.7	45	43	1.1	Dobutamine	Alive
7	F	4.3	3.3	21	32	3.3	Dobutamine, O_2	Alive
8	M	14.8	3.1	36	26	3.2	Digoxin	Alive
9	F	14.8	6.6	45	20	3.8	Dobutamine, nitroprusside	Alive
10	F	6.3	5.3	26	17	1.7	Nitroprusside	Alive
11	M	4.5	3.6	50	18	8.9	Room air	Dead
			4.2	57	18	9.3	PGE_1	
			4.4	38	12	5.9	Nitroprusside	
			6.5	30	16	2.3	Nitroprusside, O_2	
12	M	17.3	2.0	18	10	4.0	Room air	Alive
13	F	3.3	4.4	35	20	4.5	Nitroprusside, O_2	Dead
14	M	5.8	4.0	32	30	0.5	Digoxin, captopril	Alive
15	M	5.9	3.3	15	9	1.8	Digoxin, hydralazine	Alive
16	M	15.4	4.2	25	17	1.9	Digoxin	Alive
17	F	12.9	3.0	38	32	2.0	General anesthesia, O_2, dobutamine	Alive
18	M	0.7[a]	...	...	...	...	...	Dead
19	M	14.5	2.2	16	15	0.5	Digoxin, captopril	Alive
20	F	18.9	1.6	40	34	3.8	Dobutamine, nitroprusside	Alive
21	F	18.0	2.8	30	20	3.6	Room air	Alive

[a] Catheterization was not performed.

PGE_1 = prostaglandin E_1.

Material and Methods

Twenty-one children (13 male, 8 female) ranging in age from 6 months to 18.9 years (average age, 11.2 years) underwent orthotopic cardiac transplantation at our institutions between June 1985 and December 1988 (Table 1). End-stage dilated cardiomyopathy was diagnosed in 16 patients and was thought to be familial in 2 of them; hypertrophic cardiomyopathy with congestive heart failure was present in 2 children; and end-stage cardiac failure in association with congenital cardiac anomalies was present in the remaining 3 patients. Eighteen of the 21 children survived transplantation to hospital discharge and were followed from 5 to 49 months (average follow-up, 24 months).

Immunosuppressive therapy was begun in each patient two to four hours before transplantation by the oral administration of 4 to 6 mg/kg of cyclosporine and 2.5 mg/kg of azathioprine (Table 2). Intraoperatively, approximately 10 mg/kg of methylprednisolone was delivered in a bolus at the beginning of cardiopulmonary bypass. The postoperative immunosuppression regimen consisted of cyclosporine (6 to 30 mg/kg/day), azathioprine (2.0 to 3.0 mg/kg/day), and prednisone (tapered schedule beginning at 1.0 mg/kg/day) (see Table 2). The cyclosporine dose was adjusted to a trough level of 200 ng/mL by high-performance liquid chromatography on the basis of frequently obtained (two to three times per week) whole blood cyclosporine levels and evaluation of renal function (serum levels of electrolytes, blood urea nitrogen, and creatinine). In the older patients, cyclosporine was administered twice daily. In the 6-month-old patient, persistently low cyclosporine levels on a twice-daily regimen were rapidly corrected by administration of the drug three times per day. The azathioprine dose was modified to maintain a total white cell count greater than 4,000/μL in all patients. Prednisone was gradually tapered over a 12-month period from 1.0 mg/kg/day to 0.4 mg/kg/day by 6 months and to 0.20 mg/kg/day by 1 year according to a protocol devised for pediatric renal transplant patients at the University of Minnesota [12].

In addition to this immunosuppression schedule, all patients received only cytomegalovirus-negative blood

Table 2. Immunosuppression Regimen

Drug	Dosage	
	Perioperative	Postoperative
Cyclosporine	4–6 mg/kg by mouth	6–30 mg/kg/day in divided doses twice or three times a day
Azathioprine	2.5 mg/kg by mouth	2.0–3.0 mg/kg/day in single dose
Methylprednisolone	10 mg/kg intravenously as bolus, beginning of bypass	. . .
Prednisone	. . .	1 mg/kg/day in divided doses; 0.5 mg/kg/day at 3 wk in divided doses; 0.4 mg/kg/day at 6 mo in divided doses; 0.35 mg/kg/day at 9 mo in divided doses; 0.2 mg/kg/day at 12 mo in divided doses; 0.2 mg/kg/day after 12 mo once daily

both during pretransplantation evaluation and perioperatively. Prophylactic sulfamethoxazole-trimethoprim (Bactrim) was administered twice daily perioperatively and once daily thereafter. Nystatin was administered orally four times daily to suppress fungal growth.

Each of the older children has undergone endomyocardial biopsy on an outpatient basis every other week for the first 3 months, monthly for the next 3 months, and quarterly thereafter, as do the adult patients at our institution. Our infant patient underwent myocardial biopsy without incident on a same-day-admission basis approximately every other month for the first year after transplantation. Same-day magnetic resonance imaging of the myocardium for determination of myocardial water content was performed in this instance, and the patient is now followed primarily by magnetic resonance imaging [13]. We have used biopsy criteria developed at our institutions [14] to determine the presence of rejection. Specifically, the presence of a focal subendocardial or interstitial lymphocytic infiltrate has not necessitated antirejection therapy. Patients are not treated for rejection unless a diffuse mononuclear infiltrate is found on endomyocardial biopsy.

A complete set of blood, urine, and throat cultures for bacteria, virus, and fungus as well as viral serology for cytomegalovirus, herpes, varicella, and Ebstein-Barr virus was obtained as part of the pretransplantation evaluation and at yearly intervals after transplantation. Evaluation of unexplained fever has routinely consisted of examination; throat, urine, and blood cultures for bacteria and viruses; and determination of viral serology. Fever of unknown origin has been evaluated on either an outpatient or inpatient basis, depending on the age and clinical appearance of the patient and the time from transplantation. For this study, all culture-proven infections of blood, urine, sputum, or skin that occurred in the presence of clinical illness have been reported.

Results

Three operative deaths occurred in our combined experience (see Table 1). Two children and 1 infant died within 1 week of transplantation of elevated pulmonary vascular resistance and associated failure of the donor right ventricle. Patient 11 had undergone catheterization on three occasions within the last year of his life in attempts to medically decrease the pulmonary resistance. The combination of sodium nitroprusside and 100% inspired oxygen appeared to successfully lower the resistance to within acceptable limits. He died within 24 hours of transplantation of low cardiac output from right ventricular failure. Preoperatively, patient 13 had modestly elevated pulmonary arteriolar resistance but, because of right ventricular failure, required extracorporeal membrane oxygenator support after cardiac transplantation to maintain cardiac output. After five days, extracorporeal membrane oxygenation was discontinued, but the patient died two days later of low cardiac output and pulmonary hemorrhage. Patient 18 was seen in cardiogenic shock, was placed on extracorporeal membrane oxygenation, and underwent cardiac transplantation without cardiac catheterization. This patient had sustained a large pulmonary hemorrhage before transplantation, was unable to be weaned from cardiopulmonary bypass, and died intraoperatively. None of these 3 patients had evidence of rejection or infection at postmortem examination.

The 18 remaining patients were discharged six to 79 days (average period, 18 days) after transplantation. The longest hospitalization occurred in a patient who required extensive physical rehabilitation from neurological dysfunction incurred probably during a pretransplantation arrest.

Acute myocardial rejection has occurred in 7 patients on 12 separate occasions and has been responsible for the two late deaths in our combined series (Table 3). A total of nine episodes of rejection developed in 5 patients within the first 7 months after transplantation and a total of three episodes of rejection in 2 patients 2 to 3 years after transplantation. Each episode was documented by endomyocardial biopsy findings of a diffuse lymphocytic infiltrate in each biopsy specimen as previously reported [14]. Myocyte necrosis was not considered necessary for diagnosis or treatment.

Eight (67%) of the 12 episodes of rejection occurred in the presence of low cyclosporine levels. Six of these episodes were in 5 adolescents who stopped immunosuppressive medications or began ingesting alcohol or both. In these instances, cyclosporine levels fluctuated widely

Table 3. Rejection Episodes

Patient No.	Age (yr)	Time After Transplantation (mo)	Cyclosporine (ng/mL)	Treatment	Outcome
1	18.2	35.1	56–91	Solu-Medrol, antilymphocyte globulin	Died
3	18.2	31.6	74	Solu-Medrol	Resolved
	18.3	33.6	66	Solu-Medrol, prednisone	Resolved
6	16.5	3.7	41–217	Solu-Medrol	Died
10	6.4	0.8	152–305	Solu-Medrol	Resolved
17	13.3	4.6	85	Solu-Medrol	Resolved
	13.4	5.8	89	Prednisone	Resolved
19	14.5	0.2	214	Solu-Medrol	Resolved
	15.0	6.2	58–403	Solu-Medrol, methotrexate	Resolved
21	18.1	0.8	735	Solu-Medrol	Resolved
	18.2	1.8	261	Prednisone	Continuing rejection
	18.2	2.8	242	Solu-Medrol	Resolved

during the immediate prerejection period. Two of the 5 adolescents died of arrhythmias related to myocardial dysfunction and continuing rejection. Two episodes of rejection occurred in a single patient in whom cyclosporine levels had been purposely lowered to reverse renal failure. Rejection resolved, and renal function returned after 6 months of dialysis. The four remaining episodes of rejection occurred in the presence of consistently appropriate cyclosporine levels. The actuarial freedom from rejection 1 year after transplantation is 73%.

Treatment of the initial episode of acute rejection in all 7 patients consisted of intravenous administration of 15 to 20 mg/kg/day of Solu-Medrol (methylprednisolone sodium succinate) as a bolus for three consecutive days. Intravenous administration of antilymphocyte globulin was additionally given on one occasion to 1 of the 2 adolescents who subsequently died. A second episode of rejection occurred in 4 patients and was treated by augmentation of oral prednisone with rapid taper in 3; 1 of these 3 patients additionally underwent a second course of intravenous steroid therapy. The fourth patient received methotrexate in addition to Solu-Medrol for recurrent rejection. A single patient had three episodes of rejection, the third episode treated successfully with Solu-Medrol. No other increases in immunosuppressive medications for suspected, but unproven, rejection has occurred during follow-up. Rejection resolved in 5 of the 7 patients as demonstrated by biopsy findings. Continuing rejection was demonstrated in 1 patient at postmortem examination. Postmortem examination was not permitted in the second patient, but noninvasive variables had continued to suggest rejection before death.

There have been no perioperative bloodborne bacterial, viral, or fungal infections in our patients and no deaths due to infection (Table 4). Bacteremia has occurred late in 2 patients, in each instance in association with an identifiable locus of infection. Pneumococcal bacteremia in association with acute sinusitis was identified and treated with intravenous and oral antibiotics in a 2-year-old child 18 months after transplantation. Bacteremia in association with acute appendicitis occurred 21 months after transplantation in a 17-year-old boy and was successfully treated by appendectomy and intravenous ampicillin, clindamycin, and cefotaxime sodium. Cytomegaloviremia occurred 1 month after transplantation in a 16-year-old boy and was successfully treated with acyclovir. Cytomegalovirus hepatitis occurred late in 1 patient and was treated with ganciclovir successfully. Herpes was identified in the sputum and skin of 1 patient and the skin of a second. Both responded to oral acyclovir. Presumed varicella developed 1 year after transplantation in 1 child. The parents reported its occurrence only after its resolution; the child received no treatment for it. In 1 patient pneumonia developed 6 months after transplantation. All cultures, including those from specimens obtained at bronchoscopy, were negative. This patient recovered without long-term antibiotic treatment. *Candida* esophagitis developed in 1 patient 11 months after transplantation and resolved with oral Mycostatin (nystatin). There have been no other episodes of suspected, but unproven, infection treated by long-term intravenous antibiotics. Actuarial freedom from serious bloodborne infection is 83% at 1 year. Actuarial survival for our operative survivors is 94% at 1 year and 78% at 3 years.

Comment

In our experience, cardiac transplantation has a low operative mortality in critically ill children with end-stage cardiomyopathy when there is little or no evidence of pulmonary vascular disease or other organ-system failure. Our three operative deaths each occurred as a result of donor right ventricular failure in patients who had evidence of elevated pulmonary vascular resistance. In spite of recent reports of successful transplantation with higher pulmonary arteriolar resistance [15], our recent experience has reinforced for us the importance of accepting children as candidates for cardiac transplantation only if their indexed pulmonary arteriolar resistance can be pharmacologically reduced to 4 Wood units or less.

Although the number of patients in our series is small, age at the time of transplantation appeared to influence

Table 4. Infections

Patient No.	Age (yr)	Time After Transplantation (mo)	Organism, Site	Treatment	Outcome
2	15.3	1	CMV, blood	Acyclovir	Resolved
3	17.3	20.7	Streptococcus, blood; *Escherichia coli,* blood	Appendectomy, ampicillin, clindamycin, cefotaxime	Resolved
4	2.05	18.2	*Streptococcus pneumoniae,* blood	Pencillin, Augmentin (amoxicillin/clavulanate potassium)	Resolved
6	16.2	0.2	CMV, sputum	Acyclovir	Resolved
			Herpes simplex, skin	Acyclovir	Resolved
12	18.2	11	*Candida* esophagitis	Mycostatin	Resolved
	20.5	39	CMV hepatitis	Ganciclovir	Resolved
14	6.3	6	No organism found, pneumonia	Broad-spectrum antibiotics for 3 days	Resolved
15	6.9	12	Varicella	None	Resolved
21	18.7	8	Herpes simplex, skin	Acyclovir	Resolved

CMV = cytomegalovirus.

operative outcome. Operative survival for infants less than 1 year of age was 50% (1/2 patients); for children 1 to 12 years of age, 67% (4/6 patients); and for adolescents, 100% (13 patients).

Triple-drug immunosuppression appears to have favorably influenced both the perioperative and long-term courses of our pediatric patients after cardiac transplantation. Actuarial survival of the 18 operative survivors is 94%, 94%, and 78% at 1, 2, and 3 years, respectively.

This form of immunosuppression management was introduced at the University of Minnesota in 1983 [16], and since that time, more than 250 patients at our two institutions have received this therapy. In the pediatric patients, acute myocardial rejection has occurred on 12 occasions; in 67% of these instances, cyclosporine levels were subtherapeutic. Seventy-five percent of our rejection episodes occurred in the first 7 months after transplantation. Five (56%) of the nine episodes of early rejection and all of the episodes occurring after 1 year were associated with subtherapeutic cyclosporine levels.

In our series, rejection appeared more common in adolescent patients (11/12 episodes) than in children (1/12 episodes) or infants (no episodes). If all episodes within the first year are considered, the incidence of rejection for our group of patients is 0.5 episode/patient/year; if only episodes in the presence of adequate cyclosporine levels are considered, the incidence falls to 0.22 episode/patient/year. Because each episode of rejection was documented by endomyocardial biopsy and because only these episodes were treated, the incidence of rejection reported here appears to us to represent an accurate estimate for children receiving this immunosuppression regimen. In contrast to published experiences indicating that rejection occurs in the majority of children who are long-term survivors after cardiac transplantation [6, 7], the majority of ourpatients are rejection free within the first year after transplantation.

Similarly, as is known with adult patients [3], the incidence of serious infection to date appears to be low with cyclosporine added to the immunosuppression regimen, and in our experience, infections do not necessarily occur only early after transplantation. We have experienced no perioperative bacteremias, viremias, or fungemias and no deaths attributable to infection. Late bacterial sepsis has occurred in 2 children, each of whom had an identifiable locus and was successfully treated with standard antibiotic therapy. Cytomegaloviremia and cutaneous herpes have responded to acyclovir. Presumed varicella was tolerated by 1 youngster 1 year after transplantation without treatment. Infection appeared to occur in all age groups with no predisposition to any particular group (infant, child, or adolescent).

The low incidence of infectious complications in our pediatric patients echoes the results reported previously in adults [3] and, more recently, infants [9] who have received triple-drug immunosuppression after cardiac transplantation. Although this decreased incidence of infection coincides with the onset of cyclosporine usage, Andreone and co-workers [3] noted, and we concur, that the use of cytomegalovirus-negative blood as well as acyclovir and Bactrim prophylaxis most probably contributed to the favorable early posttransplantation reduction in infectious complications. Our postoperative management has also included extubation and line removal at the earliest possible opportunity to minimize the risk of infection.

Orthotopic cardiac transplantation appears to be an acceptable treatment for end-stage cardiomyopathy when no alternative exists. The operative mortality is low in the absence of pulmonary vascular disease. Triple-drug immunosuppression has remarkably reduced the incidence of both rejection and infection after transplantation in our children and has thereby improved their long-term survival. Although the eventual outcome of this therapeutic regimen is unknown, it has proved safe over our reported follow-up. Of considerable concern is the occurrence of late acute rejection in 2 adolescents who discontinued the antirejection medications. This phenomenon has accounted for the only two late deaths and 40% of all deaths in our series. Clearly, strong and consistent psychological support and follow-up are necessary in young patients, particularly the adolescent boy who, with the return of good cardiac health, often unilaterally will manipulate or discontinue medications or engage in other behavior that poses a threat to his life. This group notwithstanding, the remarkable return of these children to good health and the low incidence of hospitalization for major infection or rejection after transplantation have encouraged us to continue to recommend cardiac transplantation when no other medical or surgical therapy is available.

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DISCUSSION

DR GEORGE C. LINDESMITH (President): I was interested in your difficulty with the extremely young infants. Are you continuing with efforts in that particular group of patients?

DR LAWRENCE H. COHN (Boston, MA): You mentioned that 3 patients died of pulmonary hypertension. Do you think this was a missed diagnosis, or did these patients have more or less reactive pulmonary hypertension? Perhaps you mentioned this, but would they have been better treated by heart-lung transplantation?

DR STEVEN GUNDRY (Loma Linda, CA): I have one question. At Loma Linda, we have tried to define children as being 12 years of age or less to eliminate some misconceptions. Those older than 12 years are not different from adult transplant recipients. I wonder if you broke down your data by age, ie, children, who are patients younger than 10 or 12 years, and adults, whom we consider to be older than 12 years. If so, how did the children fare versus the adults? Certainly my 10-year-old daughter thinks that she is an adult already and seems to behave that way.

DR BRAUNLIN: In answer to the first question, we have attempted transplantation in only 1 infant less than 1 year of age in Minnesota and 1 at Washington University in St. Louis. Several others have been evaluated, but, as the people from Loma Linda are well aware, they are usually critically ill infants, and many of them have died before transplantation can be performed.

We are continuing to evaluate children with cardiomyopathy and children with hypoplastic left heart syndrome in whom the Norwood procedure for one reason or another has not been an option.

The 3 patients who had pulmonary hypertension are an interesting group, and 2 would almost certainly not be considered candidates for transplantation by our surgeons now. One infant was in extremis and on extracorporeal membrane oxygenator support. Even though catheterization studies had not been done, he underwent transplantation because there was an in-house donor available. A second child had multiple catheterizations and multiple medical maneuvers to decrease pulmonary hypertension, but most of the indexed pulmonary arteriolar resistance values obtained at catheterization were about 6 Wood units. He almost certainly would not be accepted as a candidate now, either. The third, who had moderate pulmonary hypertension, was the patient who required extracorporeal membrane oxygenation after transplantation. That was more of a surprise, and this patient might well be included in any series we began today.

We did not divide our patients into those less than 10 years of age and greater than 10 years of age. We were surprised to find that the adolescent boy was a particularly vulnerable individual in terms of medical compliance, and we think that this category of patient might form more of an at-risk group than any other in our series.

Survival After Conservative Resection for T1 N0 M0 Non-Small Cell Lung Cancer

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Two hundred forty-four veterans, with a mean age of 62.4 years, mainly asymptomatic (pulmonary), were admitted generally for other disease or pension evaluation and underwent lobectomy (131), segmentectomy (107), or wedge resection (6) for T1 N0 M0 lung cancer between 1966 and 1988. Conservative resection was preferred during the past decade. The average lesion diameter was 2 cm. Thirty-day mortality was 2.9%, similar for the three procedures. Absolute 5-year survival, 51%, was 78% if only deaths from the initial lesion are considered; 19% died of comorbidity, and 8% died of second lung cancers. Routine preoperative computed tomographic staging and intraoperative sampling of even normal-sized hilar and mediastinal nodes, conducted after 1982, improved survival ($p < 0.006$). Patients with lesions less than 2 cm in diameter (146) did better ($p < 0.04$), and those with squamous tumors improved similarly ($p < 0.02$). Lesions that communicated with a bronchus (88) were more malignant than those (156) that did not ($p < 0.02$), because from that locus undifferentiated nonsquamous tumors metastasized widely. These results suggest that the T1 N0 M0 category is not uniform. Histology, size, and location in the lung are significant variables. Results of conservative resection were similar or better than those of lobectomy. The latter was used more in deep-seated lesions, however, when major intersegmental planes were transgressed, and before modern preoperative and intraoperative staging. The T1 N0 M0 category should include lesions 2 cm or less in diameter as a discrete entity.

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Excision remains the best hope for cure of lung cancer. Unfortunately, in most patients the cancer has spread too far; others cannot be operated on because they are unfit, often from smoking. In a series of elderly veterans, routine roentgenograms were performed at hospitalization until 1986 and subsequently during medical, preoperative, or pension evaluations. Many usually asymptomatic, malignant, pulmonary nodules were evaluated. Because most of these patients had sought help for other complaints, their health was more impaired than usual with an "early" lesion. To extend operability and obviate respiratory failure postoperatively, we increasingly have used segmentectomy or rarely wedge resection whenever the tumor was staged intraoperatively as T1 N0 M0. Earlier, lobectomy was the standard procedure, and it is still used if the carcinoma is deep-seated or near the takeoff of the segmental bronchus or, occasionally, when a peripheral nodule is situated across major intersegmental planes.

Because conservative resection for cure of bronchogenic carcinoma is controversial [1], we have documented our 20-year experience. Many patients died postoperatively of comorbidity; therefore, survival data were generally expressed as death as a result of initial lung cancer. We were interested to determine the role of computed tomographic screening and routine intraoperative staging in reducing recurrence. Finally, the large number of coin lesions and the excellent follow-up in the Veterans Administration enabled us to question uniformity within the T1 stratum. The variables location, size, and histology were of particular interest.

Material and Methods

Consecutive hospital charts, pathological slides, autopsy reports, and tumor registry records of all veterans classified between 1966 and 1988 as having T1 N0 M0 lung carcinoma who were resected for cure were reviewed. All patients had been evaluated by a standard cancer protocol consisting of complete history and physical examination, routine laboratory studies, pulmonary function tests with spirometry and blood gases, sputum cytology, electrocardiogram, appropriate nuclear scans, and surgical diagnostic procedures. Preoperative pulmonary preparation included abstinence from tobacco (when possible), incentive spirometry, and bronchodilator or antibiotic therapy when indicated. Noninvasive in situ lesions were excluded, as were patients with previous lung cancer. Initially, only enlarged intrathoracic lymph nodes were sampled. Later, representative, segmental, lobar, and mediastinal nodes were analyzed routinely by frozen section intraoperatively. Preoperative computed tomographic scanning of the chest and upper abdomen to exclude mediastinal or systemic metastases became available simultaneously (1983).

Tumors were characterized histologically as squamous or nonsquamous on the basis of intercellular bridging, keratinization, acini, papillae, and mucin formation. The

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nonsquamous group contained patients with adenocarcinoma and large cell undifferentiated tumors or mixtures thereof; the predominant cell type was used for categorization. Degree of differentiation and scarring were noted. Each tumor was categorized pathologically into "peripheral" (not grossly arising from the bronchial tree) or "bronchial." Maximal diameter was recorded by the pathologist. Surgical technique used double-lumen endotracheal tubes, arterial monitoring, a limited thoracotomy with a short operating time, and mechanical stapling devices where applicable. None of these patients received adjuvant therapy.

Patients were evaluated in the outpatient clinic at frequent intervals. Recurrence was considered (1) local if in the ipsilateral thorax; (2) systemic if in brain, bones, liver, adrenal, or contralateral lung; or (3) a new tumor if solitary, generally with a different histology, usually arising years later in another lobe or lung. The day of death was known for all patients. Because autopsy could not be obtained in all patients, clinical, radiological, and laboratory data were sometimes used to diagnose metastases. Survivals were calculated from the day of operation using standard life-table procedures. All patients were followed using the Veterans Administration central, master index, and locator files. Data, calculations, and chart generations were performed on a Commodore C-64 Computer/1581 disk drive with Jiffy DOS (Creative Micro Designs) and Mirage Data Base (Mirage Concepts), Practicalc II (Practicorp, International), and Chartpak-64 (Abacus Software).

Results

Two hundred forty-four veterans aged 40 to 83 years (mean age, 62.4 ± 7.5 years) were studied. All but 1 were smokers; 242 were male. The majority (68%) were asymptomatic in regard to the chest. There were 131 lobectomies (53.7%), 107 segmentectomies (single, 83 [77.6%]; multiple, 24 [22.4%]), and six wedge resections (2.5%). The latter were performed for small (average diameter, 15.7 mm) nodules (squamous, 1; nonsquamous, 5) in the apical, posterior, or lingular segments in the upper lobes and in the superior segment in the lower lobes. Because most segmentectomies were performed during the past decade (Fig 1) (wedge resections are enumerated with them), their average follow-up time was only 3½ years as compared with 4½ years for lobectomies. Histology was squamous in 137 (56.1%) and nonsquamous in 107 (43.9%). The pathologist was able to trace a segmental or subsegmental bronchus grossly into the lesion in 88 (36.1%) specimens (bronchial); the remainder (156) were peripheral. Degree of differentiation was as follows: well-differentiated, 21 (8.6%); moderately differentiated, 94 (38.5%); and poorly differentiated, 129 (53%). Size distribution is shown in Figure 2; the average diameter (20.3 ± 6 mm) was similar for lobectomy and segmentectomy cases. Lesions were primarily located in the upper lobes (160 [65.5%]: right, 83; left, 77). There were 69 in the lower lobes: right, 39; left, 30; and middle, 15 (Fig 3).

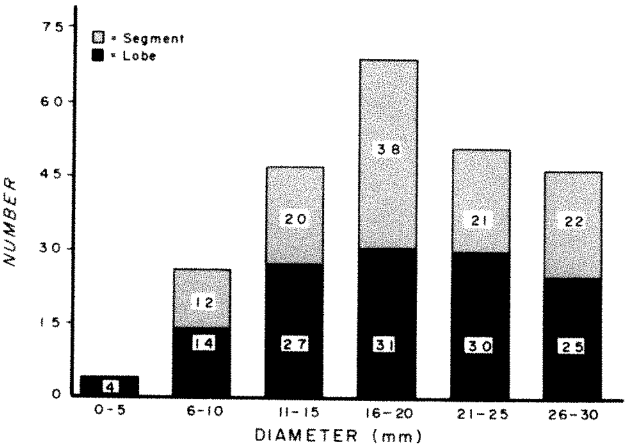


Fig 2. There was no difference in size distribution of nodules resected by lobectomy or segmentectomy. T1 N0 M0 resections (n = 244).

Tissue diagnosis was generally made at operation (69%). Cytology studies were undertaken in 68.2% of our

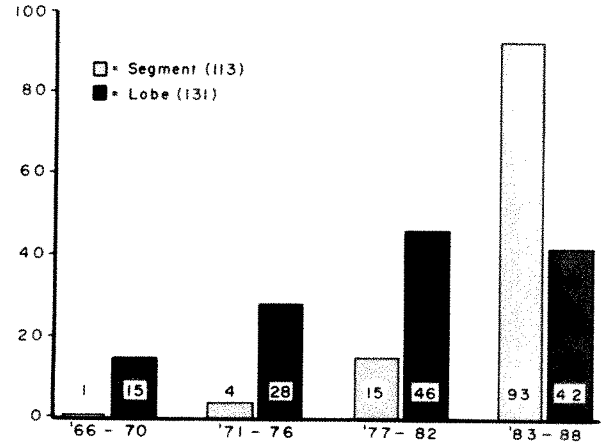


Fig 1. Relative frequency of lobectomy and segmentectomy by year. T1 N0 M0 resections (n = 244).

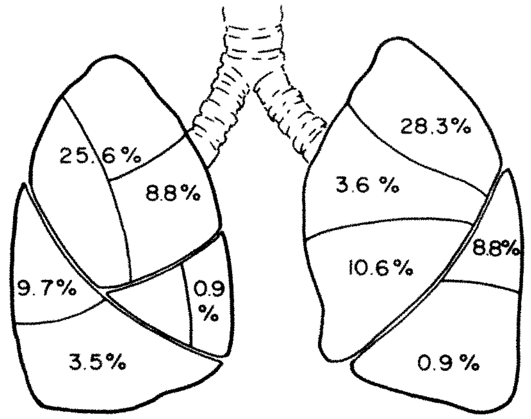


Fig 3. Anatomical distribution of segmental resections. Left lung had more resections than right lung because lingulectomy and upper division resections would be lobectomies on the right side. The few lesions in the lower lobes were localized to the superior segment. T1 N0 M0 resections (n = 113).

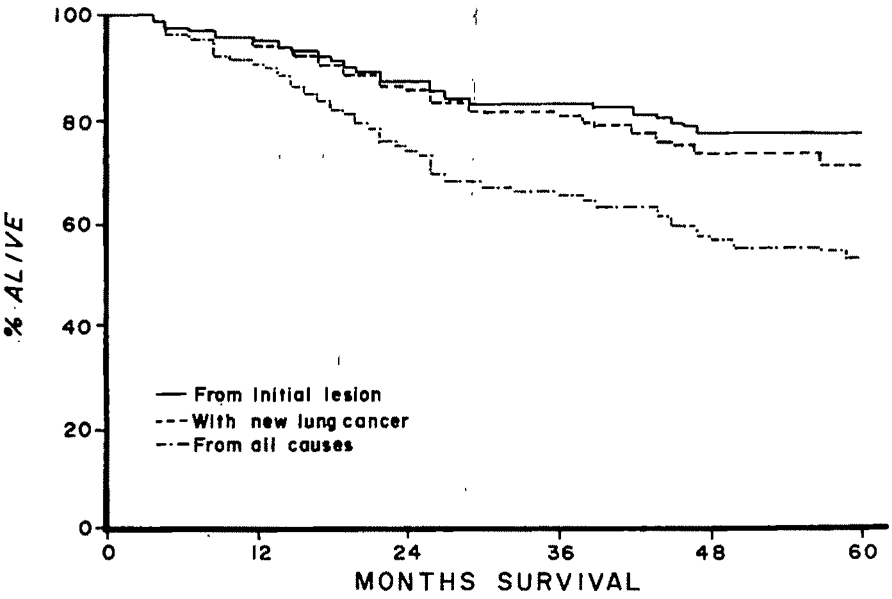


Fig 4. Overall survival from initial lesion, all lung cancers, and total deaths (n = 244). More veterans died of other causes than of their resected T1 N0 M0 lung cancer.

244 patients; bronchial washings predominated over sputa (70.2% versus 29.8%). Twenty-nine percent of cytological studies were positive. Bronchial lesions were three times more likely than peripheral lesions to have malignant cytology (50% to 17.4%). Bronchial squamous lesions were more often positive (2:1).

Operation time averaged 123 minutes (lobectomy, 144 minutes; segmentectomy, 126 minutes; wedge resection, 98 minutes). Blood loss averaged 260 mL; chest tubes remained in place for two to 24 days (average 4.3 days). Thirty-three (13.5%) patients received transfusions. The ratio of forced expiratory volume in 1 second to forced vital capacity averaged 59% for lobectomy, 56% for segmentectomy, and 48% for wedge resection. Thirty-day mortality was 2.9% (7) [segmentectomy 4 (3.5%) lobectomy 3 (2.3%)] caused by sepsis, myocardial infarction, or chronic obstructive pulmonary disease.

Overall survival (death from initial lesion) calculated by the Kaplan-Meier method (Fig 4) was 95% at 1 year, 83% at 3 years, and 78% at 5 years. There was no statistically significant difference between the two groups (Fig 5). There were 20 (8.2%) local recurrences: lobectomy, 15 (11.5%) and segmentectomy, 5 (4.4%); the latter patients underwent completion lobectomy, and 4 remain well. New lung cancer developed in 21 patients (8.6%): squamous, 15 (71.4%); nonsquamous, 3 (14.3%); and small cell, 3 (14.3%). Six patients (28.6%) had a second operation: lobectomy, 4 (66.7%); segmentectomy, 2 (33.3%). Fourteen (66.7%) died. Causes of death other than lung cancer and operative mortality were cardiovas-

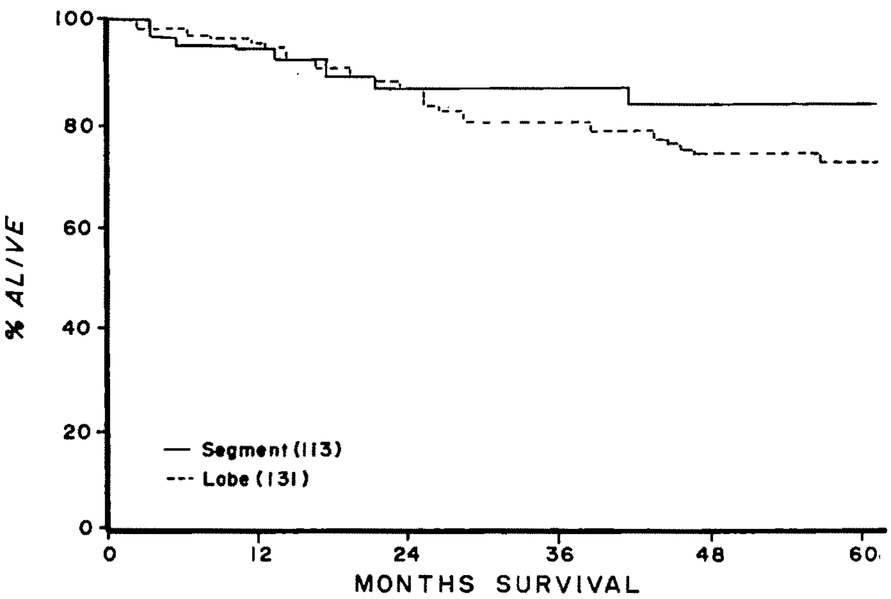
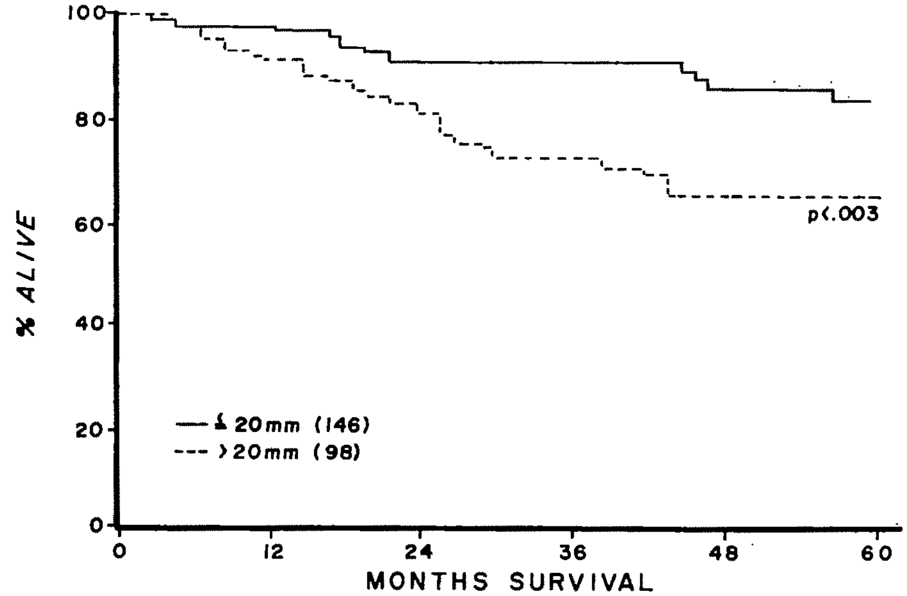


Fig 5. Survival of segmentectomy of group as compared with lobectomy group. (deaths resulting from initial lesion only). T1 N0 M0 resections (n = 244).

Fig 6. Patients with small tumors had better survival (initial lesion). T1 N0 M0 resections (n = 244).



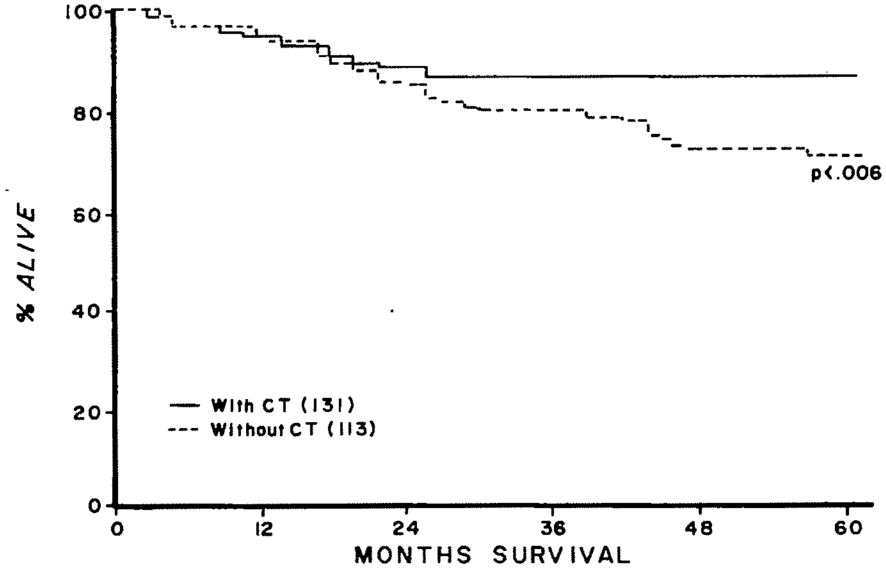
cular disease (30%), other cancers (23%), chronic obstructive pulmonary disease (14%), and miscellaneous (33%). Seventy percent of patients dying of their primary lung cancer had systemic spread (one fourth had isolated brain metastases).

Size greater or less than 2 cm affected survival (Fig 6). Routine preoperative computed tomographic staging and intraoperative sampling of even normal-sized hilar and mediastinal nodes improved prognosis (Fig 7), even in small cancers (Fig 8) ($p < 0.04$). Squamous histology was more favorable than nonsquamous (Fig 9). Nonsquamous deep-seated (bronchial) tumors were very malignant (Fig 10), especially the undifferentiated type. Peripheral undifferentiated nonsquamous lesions had better survival characteristics, similar to those of squamous or differentiated nonsquamous tumors (73%, 67% at 5 years) (Fig 11). Scarring (histological) of the lesion could not be related to survival.

Comment

Churchill and colleagues, by performing the first lingulectomy [2] and later breaking the dogma of using only total pneumonectomy for bronchogenic carcinoma [3], pioneered conservative resection. The technique of segmental resection was refined by Overholt and Langer [4] and Chamberlain and Klopstock [5] in patients with bronchiectasis or tuberculosis. In 1972, both Bonfils-Roberts and Clagett [6] in this country and Le Roux [7] in England reported series of segmentectomy for primary lung cancer. This procedure was used in the elderly and also either when "the lesion palpated at thoracotomy was thought to

Fig 7. Significant difference in survival (initial lesion) of patients occurred after 1983 when both routine computed tomography (CT) and intraoperative staging of even normal-sized lymph nodes were instituted. T1 N0 M0 resections (n = 244).



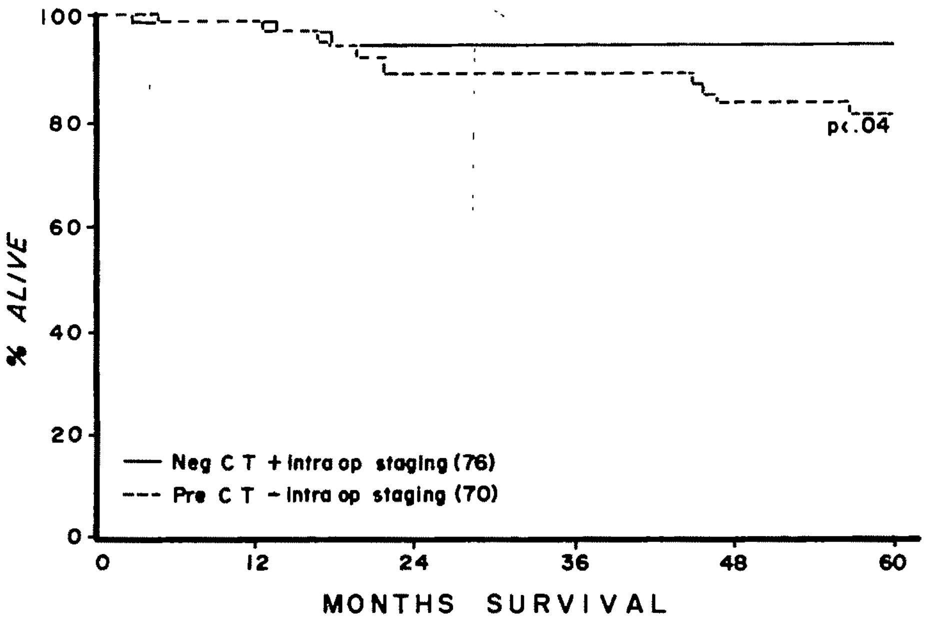


Fig 8. Survival from initial lung cancer in patients with small cancers less than or equal to 2.0 cm in diameter (n = 146) with or without both computed tomography (CT) and intraoperative staging.

be tuberculous, because the segment in which the tumor lay was separated from adjacent lung by an anatomically complete fissure or to avoid unnecessary limitation of an already diminished respiratory reserve" [7]. Mortality was minimal and some patients survived a long time. "Results seemed no worse than after more extensive resections for small tumors" [7]. The following year, Jensik summarized 123 such operations for lung cancer; 10 years later, the total was 445 [8]. Jensik [8] used the procedure in patients who had had previous lung excision, for palliation in stage III disease, and for cure in individuals with peripheral stage I and II cancer and compromised cardiorespiratory status. Steele and colleagues [9] and Shields and Higgins [10] reported minimal resections (segment or wedge) in veterans.

Other surgeons' experiences have been summarized [11–15]. Anxiety over local recurrence (5% to 25%) led some investigators [16] to consider segmentectomy inferior to lobectomy for cure of primary lung cancer and as justifiable only in aged patients with limited life expectancy in whom T1 N0 M0 disease is common [17]. However, we showed that completion lobectomy can be performed successfully. Some of these relapses may actually have been unrecognized synchronous tumors [18], new-onset metachronous cancers [19], or even metastatic adenocarcinoma from the abdominal viscera or squamous cell malignancy spreading out of the upper respiratory tract or esophagus. Furthermore, many of these series included cases of peripheral small cell T2 or N1 disease and cases of tumors crossing a fissure. Cure was not always distin-

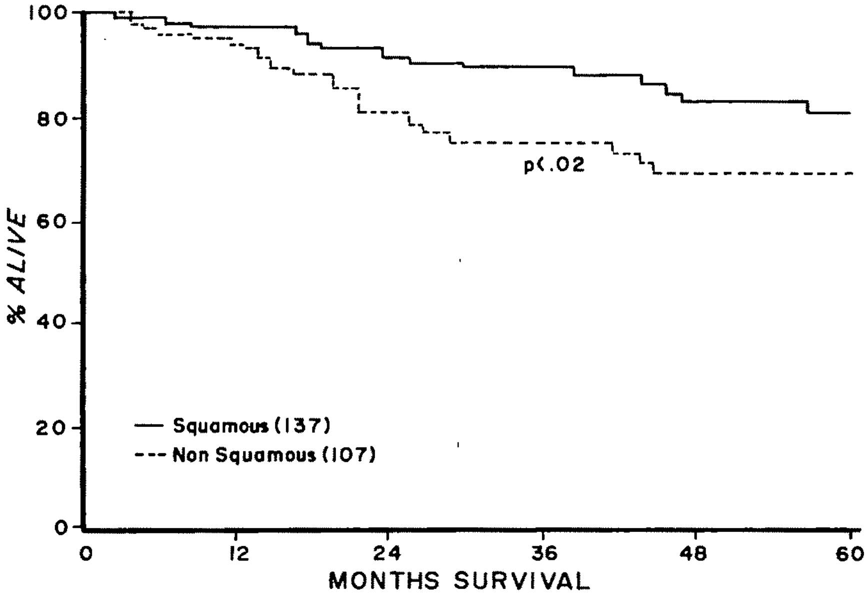
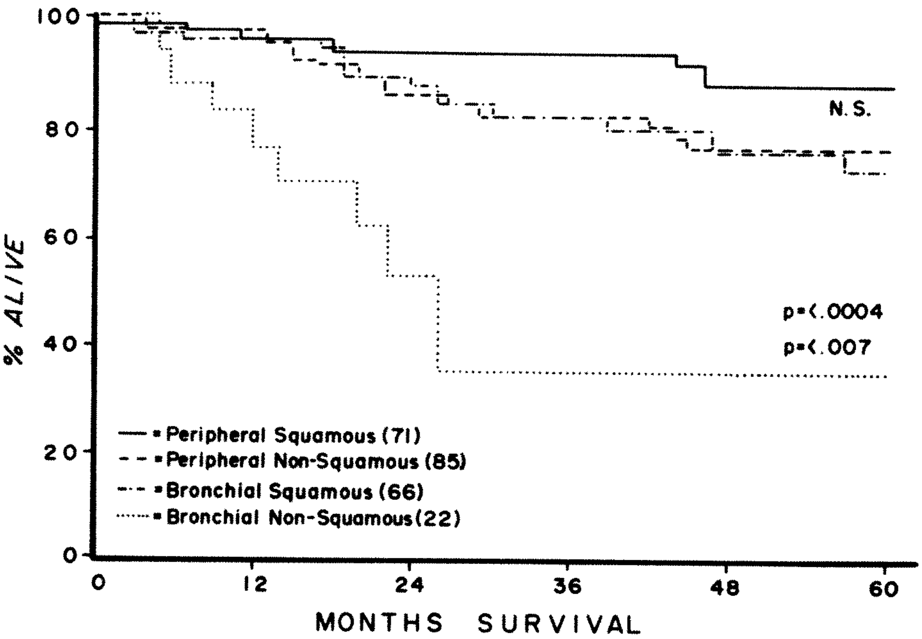


Fig 9. Patients with squamous cell lesions did better after resection than patients with nonsquamous histology. T1 N0 M0 resections (n = 244).

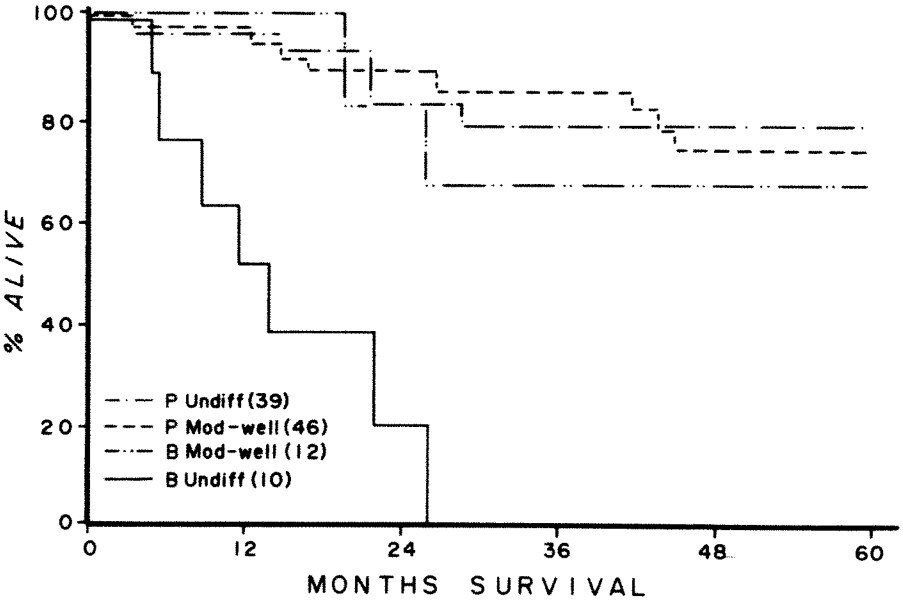
Fig 10. T1 N0 M0 lesions (n = 244) that grossly communicated with a segmental or subsegmental bronchus (bronchial) had a worse prognosis than those that did not (peripheral), despite a predominance of the less malignant squamous cell histology in the former.



guished from palliation because intraoperative staging to rule out invasion of the viscera (T2) and pleura (T3) or mediastinum (T3 or N2) had not been performed. Retrospective comparisons between lobectomy and segmentectomy, wedge resection [20], or lumpectomy [21] showed similar mortality and morbidity, as in our experience. Segmental resection had originally been associated with bronchopleural fistulas. We prefer segmentectomy to wedge resection, as do other investigators [8, 13], because it, being anatomical, conserves lung substance, allows lymph node staging, removes a sizable margin of bronchus, and is mandatory in more centrally located tumors.

The primary concern was whether long-term survival would be as good as after lobectomy. Shields and Benfield [22] and later Jensik [8] suggested that segmentectomy should only be considered curative in T1 N0 M0 disease. Shields and Benfield [22] earlier (1973) had called for a prospective randomized trial. Ten years later, a multiinstitutional study was started; it [23] soon showed that some T1 N0 M0 lesions were unsuitable for segmentectomy because a proper margin could not be obtained in deep-seated tumors. Nearly a third of our patients required lobectomy in recent years when we were emphasizing segmentectomy. Confirming retrospective analyses, however, the incidence of postoperative complications and death was similar in the randomized groups. Respiratory failure occurred only in the lobectomy cases [23]. Long-term survival data are presently unavailable.

Fig 11. The undifferentiated nonsquamous bronchial lesions (B) are very malignant. Peripheral (P) undifferentiated nonsquamous tumors have good survival characteristics similar to those of other types of T1 N0 M0 tumors (Fig 10).



Extent of peripheral lung tumor historically has been considered an important prognostic indicator [24, 25]. Survival data [26–31] regarding T1 N0 M0 lesions have not indicated size variations within the group to be a significant variable. However, in 1969 [32] the Mayo clinic group noted that "the 5-year survival rate for 49 patients whose lesions measured 2.0 cm or less in diameter was 68.2% as compared to 46.5% for 67 lesions 2.1–3.0 cm." Steele and Buelle [33] reported in 1973 that patients with small tumors less than 2.5 cm in diameter did better. Yashar and Yashar [34] reported in 1975 on 18 patients with a tumor less than 2 cm in diameter; 61% were alive and well 5 years after operation, a significantly better outcome than that of patients with larger lesions. The Japanese recently categorized tumors less than 2 cm in diameter as "early" lung cancer. In 42 such cases, 5-year survival was 86.9%. When the diameter was less than 1.5 cm, patients did even better [35]. The present data are in agreement with these observations because they demonstrate a significantly improved survival of patients whose lesion was less than 2 cm in diameter (Fig 6). This conclusion supports researchers [28, 36] who would categorize T1 N0 M0 lesions as a separate stage as it introduces a new variant (T½) [37] within this group.

Whereas Daly and co-workers [38] suggested that computed tomography is not indicated for staging in patients with peripheral lesions less than or equal to 2 cm, Mori and colleagues [39] reported that 52 of 108 patients with small lung cancers (less than 2 cm in diameter) were eventually shown to have local or distant metastases. Computed tomography is now considered necessary for preoperative staging of all radiographic T1 lung cancer. Heavey and associates [41] found that it substantially altered therapy in 16% of such patients. Another 10% were found at thoracotomy to have microscopic metastases in normal-sized (less than 1 cm) hilar or mediastinal lymph glands. Our own data (Fig 7) confirm the importance of computed tomographic preoperative screening of thorax and abdomen combined with intraoperative sampling of even normal-appearing segmental, bronchial, hilar, and mediastinal nodes. This beneficial effect was apparent even in small cancers (2 cm or less) (Fig 8). When bronchial or mediastinal nodes were invaded, "curative" lobectomy or palliative segmentectomy was used [12].

Matthews [42], from autopsies in veterans who died soon after curative resection for unstaged lung cancer, documented the importance of asymptomatic systemic spread. She pointed out that nonsquamous cell carcinoma was more prone to metastasize. Nevertheless, some researchers believe [30] that if proper preoperative and intraoperative staging is done, survival of patients with non-small cell T1 N0 M0 disease is not influenced by histology. However, the Lung Cancer Study Group [43], who adhered to standardized staging criteria, found recurrence and death rates to be lower for patients with pure squamous cell rather than nonsquamous or mixed histology, despite inclusion, unlike in our series, of women who had a higher proportion of the more benign alveolar cell variant [27]. Our experience is similar (Fig 9). Our patient population did have more squamous than nonsquamous lesions, which is true of most studies of veterans [20], who are heavy smokers [36]. Furthermore, we found that patients with subpleural T1 N0 M0 adenocarcinoma have survival characteristics comparable with the excellent prognosis of both bronchial and peripheral squamous cell lesions (Fig 10). When undifferentiated nonsquamous cancer grossly invades segmental or subsegmental bronchi (and presumably the accompanying vasculature), however, it is much more likely to spread throughout the body. It is perhaps this entity (Fig 11) that has given deep-seated or central lesions a bad name [38] despite their early (T1 N0 M0) stage. Thus, undifferentiated tumors that would be expected [44] to be more malignant were not so in our experience, with the important exception of the bronchial nonsquamous type. The concept that undifferentiated lung cancer is of enhanced malignancy has been controversial [26–31]. Unlike Shimosato and colleagues [45] and other researchers [35], we were unable to prognosticate on the basis of scarring.

Use of lobectomy rather than segmentectomy for removal of deep-seated tumors, as well as for lesions crossing major intersegmental planes, along with its almost routine application before the advent of modern staging (with consequent longer follow-up) is presumably the reason why the recurrence rate in our experience paradoxically was higher in the more radical procedure. There was no attempt to randomize the operations. Most deaths from lung cancer result from distant spread [46]. The brain is a common (sometimes the only) site, especially with adenocarcinoma. We, like most thoracic surgeons, do not routinely use computed tomographic scans of the head because of the meager yield in the absence of signs or symptoms elicited from a careful history and neurological examination [47]. A few silent metastases will be missed, however [48]. Perhaps newer isotope scans using labeled monoclonal antibodies will be more cost-effective [49].

Our data show that the T1 N0 M0 category is not uniform. Survival after curative resection is significantly influenced by comorbidity, metachronous lung cancer, and staging. Tumor factors include size, histology, and bronchial invasion. Deep-seated lesions and those located astride major intersegmental planes still require lobectomy. Conservative resection, which extends operability without increasing postoperative morbidity, can be used in the remainder with minimal risk of local recurrence.

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DISCUSSION

DR JOHN R. BENFIELD (Sacramento, CA): The title leads one to believe that the most important message in this report is the outcome of conservative resections as compared with lobectomy in the treatment of T1 N0 M0 non-small cell lung cancers. The title, however, may be somewhat misleading because this is a report of a 23-year experience during which the indications for segmentectomies and the thoroughness of preoperative and intraoperative staging changed.

As compared with the previous routine use of lobectomy, during the past decade segmentectomy was considered the resection of choice. As compared with the practice, early in the series, of sampling only enlarged nodes found at operation, representative nodes of normal size were sampled routinely in the latter years of the series. Therefore, this report will not convince those who believe that lobectomy is the operation of choice for the treatment of lung cancer and who doubt the merits of previous studies in which complete resections of lung cancers by segmentectomy were reported to be as effective as lobectomy. The definitive answer to this question awaits the outcome of the Lung Cancer Study Group's protocol in which lobectomy or segmentectomy was used randomly for lesions amenable to either resection. It would surprise me if the Lung Cancer Study group's findings did not show that the use of resections less than lobectomy is quite adequate for eradicating cancers that can be cured by resection.

I accept the observation that the cure rate from resections after the advent of computed tomography (CT) was slightly better than the rate before CT, but I believe that CT is an innocent bystander, largely unrelated to the finding. The more likely explanation is the more complete preoperative and intraoperative staging with biopsies that occurred during the CT era; lymph node samplings with study of the permanent sections rather than CT assured with maximum certainty that patients included as having T1 N0 M0 cancers actually had stage 1 neoplasms.

Read and associates' definition of local recurrence is recurrence in the ipsilateral thorax or supraclavicular area. I cannot accept this definition because I believe there is ample evidence that lymph node metastasis in cancer is evidence of systemic disease. We thoracic surgeons need to keep up with this modern oncologic concept, lest we continue to focus on lymph node excision as an effective means of cancer control. As in breast cancer, melanoma, colon cancer, and other cancers, lymph node excision is, I believe, largely of prognostic value—useful for identifying patients who need systemic therapy. I would prefer that Read and associates define local recurrence as return of cancer at the margin of resection of the primary cancer.

The important and valuable contribution of this study lies in the facts that show histology, size, and location of T1 N0 M0 cancers to have significant effect on outcome. The suggestion that there be a separate staging nomenclature for cancers less than 2 cm in diameter is supported by these findings. The more aggressive nature of endobronchial cancers as compared with peripheral parenchymal lesions is noteworthy. Similarly important is the observed aggressive nature of nonsquamous cell cancers. In particular, the highly malignant behavior of large cell undifferentiated cancers is properly emphasized by Read and associates. Their findings add credence to the viewpoint of Dr Raymond Yesner, a leading pulmonary pathologist from Yale, in a recent editorial [Ann Thorac Surg 1989;47:796–7].

I congratulate Read and associates for a thoughtful, thought-provoking contribution, which I might have entitled "Clinically Relevant Subsets of Stage 1 Non-Small Cell Lung Cancers." I further congratulate them for using segmentectomy rather than wedge excision as the resection of choice for the future.

I would like to know how Dr Read and his co-authors would treat a T1 N1 M0 non-small cell carcinoma peripherally located in the apical segment of the left upper lobe in a patient with moderately severe chronic obstructive pulmonary disease.

DR THOMAS W. SHIELDS (Chicago, IL): Dr Benfield and I read the same paper and arrived at much the same conclusions, although not entirely.

I think Read and associates have made two important points: (1) the smaller lesions of the T1 descriptor do better than the larger ones, and (2) a segmentectomy is an adequate cancer operation when the appropriate criteria for selection are followed. Three criteria are (1) a small peripheral lesion, (2) a lesion that does not cross an intersegmental plane, and (3) a lack of lymph node involvement. When these criteria are met, as Dr Benfield has shown, segmentectomy is a very adequate and satisfactory operation that can be performed in good-risk patients as well as in the poor-risk patients.

The smaller T1 lesion has a better prognosis than the larger one. This has been shown to be true in the T2 group by numerous investigators in the past, and Read and associates have shown that it is also true in the T1 lesion group. The T descriptor was never meant to imply complete homogeneous groupings of the tumor. Actually, it was constructed so that some unity existed within each subset. I believe there would be no purpose in dividing T1s into two groups.

The apparent poorest risk group in this subset, as pointed out by Read and associates and emphasized by Dr Benfield, is the subset of patients with adenocarcinoma in the central location of the segment or lobe. These patients do poorly, and for years, I have found this to be true of adenocarcinoma in the central portion of the lung at any time; one could combine this central lesion with the central squamous cells and readily say that central tumors do worse than peripheral tumors. Therefore, a nonsquamous cell tumor in the center of the lobe that has involved the bronchus has the worst prognosis, and to characterize it thus would be more appropriate than changing the histology, saying that adenocarcinoma and squamous carcinoma are different.

Last, I would like to ask Dr Read a question. What is the basis for saying that preoperative CT has led to better results? Are the improved results not actually a byproduct of better intraoperative staging? Apparently you may have found a few occult metastases in the liver or adrenals. At most, this might be 3% but, as we heard earlier, with all stages of the disease was less than 1%. Therefore, I do not think that preoperative CT is a factor of any importance whatsoever, particularly if a true T1 N0 peripheral lesion is evident on roentgenogram.

DR MICHAEL BURT (New York, NY): Dr Nael Martini had been asked by Dr Read to discuss this paper but requested that I do so in his absence.

At our institution, we have found results strikingly similar to those of Read and associates. In a preliminary analysis of 405 patients followed prospectively with pathologic T1 N0 M0 non-small cell lung cancer treated operatively, 319 patients had lobectomy and 86 had segmentectomy. All had mediastinal lymph node dissection.

Of the 319 patients who had lobectomy, 12 (3.8%) had local recurrence, a finding very similar to those of Read and associates, except that N3 disease or supraclavicular nodes were considered metastatic disease and not local recurrence. Of the patients who underwent wedge resection or segmentectomy, we had local recurrence in 5 of 86, or 5.8%.

Our survival curves compare favorably with those of Read and associates. We had a 5-year survival of 75% overall. The lobectomy patients tended to do better ($p = 0.09$ by log-rank analysis), and we believe this results from use of lobectomy as the treatment of choice for resectable non-small cell lung cancer at our institution. Wedge resection or segmentectomy was reserved for patients with compromised pulmonary function.

An interesting and, we believe, important point of the study by Read and associates is that preoperative evaluation, including CT scanning of the chest and upper abdomen, and intraoperative nodal evaluation resulted in significant improvement in survival, almost assuredly reflecting more accurate staging. Although this study and our data suggest that the results of segmentectomy and lobectomy for patients with T1 N0 M0 non-small cell lung cancer are similar we, as Dr Benfield suggested, are awaiting results of randomized trials for confirmation.

I have one question for Dr Read: do you have a feeling for the number of patients who had their preoperative clinical stage changed by adding intraoperative nodal evaluation?

DR READ: It is a great privilege to have Dr Benfield comment on this paper because in 1973, when commenting on Dr Jensik's paper, he asked for a prospective, randomized, single-blind study of segmentectomy versus lobectomy in these cases. We all eagerly await the results of that study.

I appreciate his remarks. With regard to the best treatment for a patient with an apical-segment small lesion with positive hilar nodes and some degree of limitation of respiratory reserve, I believe a lobectomy would be curative, but some type of segmentectomy, which would be a lesser procedure, might be of benefit for such a patient. It would depend on the state of the N1 disease—whether it involved the blood supply to the lobe or whether one could perform an upper division resection in that patient and obtain better nodal clearance along with the lesion itself.

In 1978, Dr Shields, before this organization, recommended the criteria for curative resection of T1 disease using the segmentectomy procedure. Dr Shields believes that CT scanning did not add much benefit as compared with intraoperative nodal sampling. I agree. We introduced both procedures at the same time, however. As Dr Shields remarked, some patients have adrenal metastases or small lung metastases that will be picked up by CT scan. We hope that in the future monoclonal antibodies can be used with isotope labeling so that we can visualize brain metastases cost-effectively. Two of our patients died after segmentectomy with isolated solitary brain metastases.

Finally, in response to Dr Burt, who represents Dr Martini, another pioneer in the 1970s in research on conservative resection, I agree that intraoperative frozen-section analysis of a representative sample of the nodes from the hilar or mediastinal region is mandatory if you adopt this procedure.

Cervical Exenteration

Hermes C. Grillo, MD, and Douglas J. Mathisen, MD

Division of Thoracic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Cervical exenteration is a radical operation to remove the larynx, portion of the trachea, and the esophagus, and frequently requires a mediastinal tracheostomy. Highly selected patients with obstructing neoplasms of the esophagus and airway can be palliated and sometimes cured by this aggressive surgical approach. Fatal hemorrhage from pressure or exposure of the innominate artery is avoided by elective division of the artery (preoperative angiograms and intraoperative electroencephalographic control are essential), using the omentum to separate the trachea and great vessels, and removal of a bony plaque of chest wall to allow a well-vascularized bipedicled skin flap to drop into the mediastinum for the tracheocutaneous anastomosis. Eighteen exenterations were performed. Mediastinal tracheostomy was performed in 14 patients and division of the innominate artery was performed in 7. Esophageal replacement was predominantly with the left colon. Complications include esophageal leak (2 patients), stomal separation (2), transient hemiplegia (1), colonic obstruction by substernal tunnel (1), and need for prolonged mechanical ventilation (4). There was a single operative death. Postoperative survival was disease dependent. All patients achieved an excellent airway and relief from dysphagia.

(Ann Thorac Surg 1990;49:401–9)

Primary or secondary malignancies involving the upper aerodigestive system present formidable problems for patients and physicians. Because of the impact these problems have on the quality of life, careful consideration must be given not only to cure but also to palliation. Irradiation often fails to achieve these goals and complicates future treatment because of its effects on wound healing. Overzealous radiation therapy may result in destruction of the airway, esophagus, or both. Solutions for these problems must be found. Tubes and stents are one alternative but may be intolerable or unacceptable to some patients and obviously do not treat the underlying problem. If surgical alternatives are to be considered, the risk of the procedure and the expected length of survival must be carefully weighed.

Historically, radical surgical procedures involving both the cervical trachea and esophagus have been associated with high operative mortality. Massive hemorrhage from blowout of the innominate artery was a frequent cause of death. This usually resulted from tracheal stomal separation with exposure of the great vessels or pressure necrosis from the trachea. When the operation is successful, however, cure is sometimes possible and palliation substantial. Successful operations are the functional equivalent of a laryngectomy.

Cervical exenteration removes the larynx, a portion of the trachea, all or part of the esophagus, and the lower pharynx, and frequently requires a mediastinal tracheostomy. Careful patient selection and preparation are essential. We have prophylactically divided the innominate artery whenever pressure or stomal proximity might exist between the trachea and innominate artery. Preoperative angiograms identify patients with vascular disease that may preclude division of the innominate artery. The omentum is frequently used to buttress the trachea, thereby minimizing the risk of pressure against the innominate artery or exposure of the vessel if stomal separation occurs. These maneuvers appear to have eliminated the risk of fatal hemorrhage.

Material and Methods

We reviewed hospital and office records of all patients undergoing cervical exenteration at the Massachusetts General Hospital since 1969. All patients undergoing resection of the upper airway including the larynx and all or part of the esophagus were included.

Preoperative Evaluation

Because of the magnitude of the operative procedure involved, each patient must have a complete medical evaluation. Cessation of smoking is important to minimize pulmonary complications.

The extent of disease must be defined as precisely as possible. Tracheal roentgenograms help to define the extent of airway involvement. These studies have been outlined in previous reports [1]. The esophagus is assessed with barium contrast studies. Computerized axial tomography with and without contrast and magnetic resonance imaging are extremely useful in determining the extent of disease and involvement of nearby structures, especially encasement of cranial vessels. Endoscopic measurements are essential either before or at the time of operation and complement the radiological evaluation. Radiological studies to identify metastatic disease are also indicated, with special attention to direct involvement of the cervical spine.

Aortic arch angiograms should be obtained to determine whether the four arteries supplying the brain are involved either by tumor or by degenerative disease

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because division of the innominate artery may be necessary. If esophageal reconstruction is to be made with colon, superior and inferior mesenteric artery angiograms should be performed to determine the blood supply and collaterals of the bowel to ensure that adequate length of colon is available to reach the pharynx if necessary. Inadequate vascular supply will dictate alternative methods of esophageal reconstruction. Bowel preparation is done in all patients.

Operative Technique

In the majority of patients, arrangements are made in advance for electroencephalographic monitoring as needed during the operation in the event that division of innominate artery is required. Electrodes are therefore applied before induction of anesthesia so that recordings may be obtained at critical times during the procedure. The patient is intubated either orally or through an existing tracheostomy (with the tube prepared in the operative field). The patient is placed supine on the operating table; the operating field extends from the chin to the pubis. A thigh is also prepared as a source of split-thickness skin grafts. If it is believed that a venous graft will be required, allowance must also be made for this. At least one arm is usually abducted so that it will be available for arterial or venous access. A warming mattress may be advisable as the procedure may be lengthy. A nasogastric tube and a Foley catheter are placed.

The operation is usually performed with two operating teams, one for the neck and mediastinum and the other for the abdomen to prepare the esophageal replacement. If the patient has been intubated through an existing tracheostomy, the tube in place is changed to a flexible Tovell-type endotracheal tube during the preparation and connected to the anesthesia machine with sterile tubing. This tubing may be moved at will on the operative field and does not hinder the surgeon.

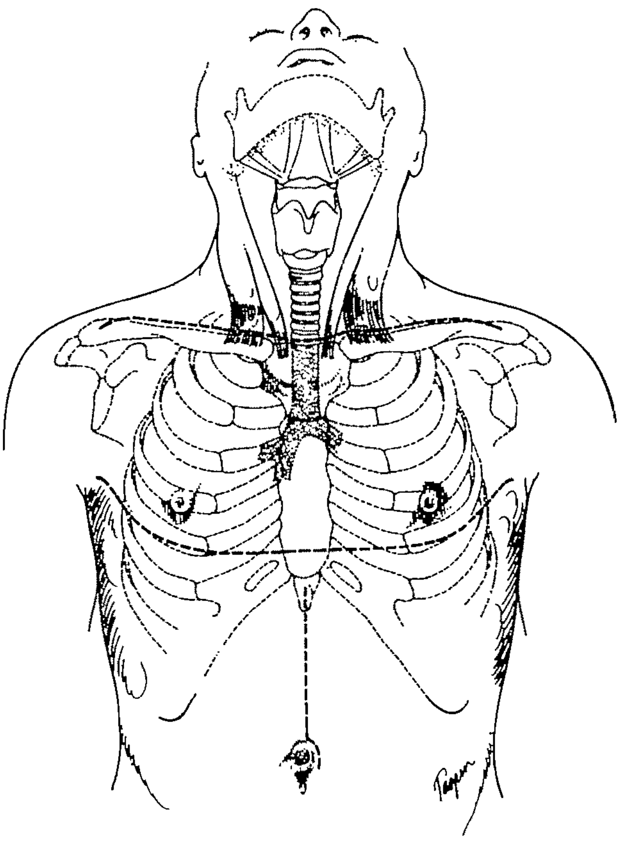

Fig 1. Skin incisions.

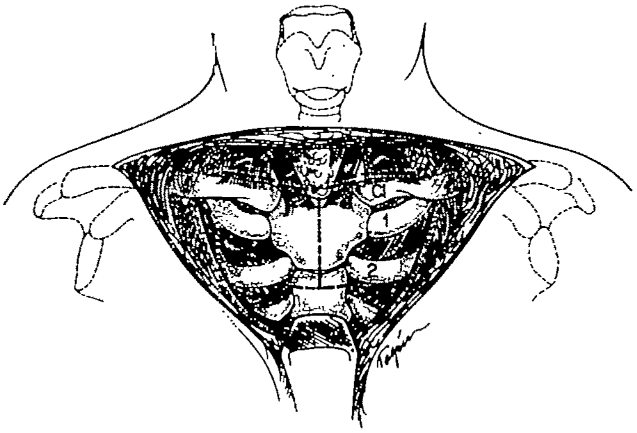

Fig 2. The inferior skin flap is elevated and the upper sternum is divided to facilitate evaluation for resectability.

Incisions are individualized, depending on existing tracheal stomas and whether tumor or severe radiation change involves the cervical tissue. In general the initial approach is a transverse incision just above the heads of the clavicles (Fig 1). This permits full exposure for exploration and, when extended, is adequate for the entire cervical dissection. The cervical exploration is conducted so that no irrevocable moves are made until the surgeon is certain that the procedure can indeed be completed. In the case of a bulky lesion such as recurrent thyroid carcinoma in which it is clear that exenteration will be complete, the dissection is carried out just medial and anterior to the carotid artery and internal jugular vein on both sides. On rare occasions, even if one of these vessels is involved, it may be excised and reconstructed. If the extent of mediastinal involvement cannot be determined adequately through the cervical incision described, the incision is extended laterally along the margin of the clavicles on either side and the inferior flap is raised over the pectoral fascia, especially in the midline (Fig 2). The upper sternum is divided and then split vertically in the midline from notch to second interspace and across the second interspace transversely (Fig 3A). Occasionally, depending on the extent of the trachea involved, this procedure may be performed through the first interspace only. Once the surgeon determines that the lesion will be removed, the abdominal team begins to mobilize the portion of bowel that will be used for esophageal reconstruction. Some patients, such as those with adenoid cystic carcinoma, require only laryngotrachiectomy without esophageal resection. Some require only removal of anterior muscular layer or both muscular and mucosal layers of the esophagus; in these patients, reconstruction is achieved by narrowing the esophageal tube.

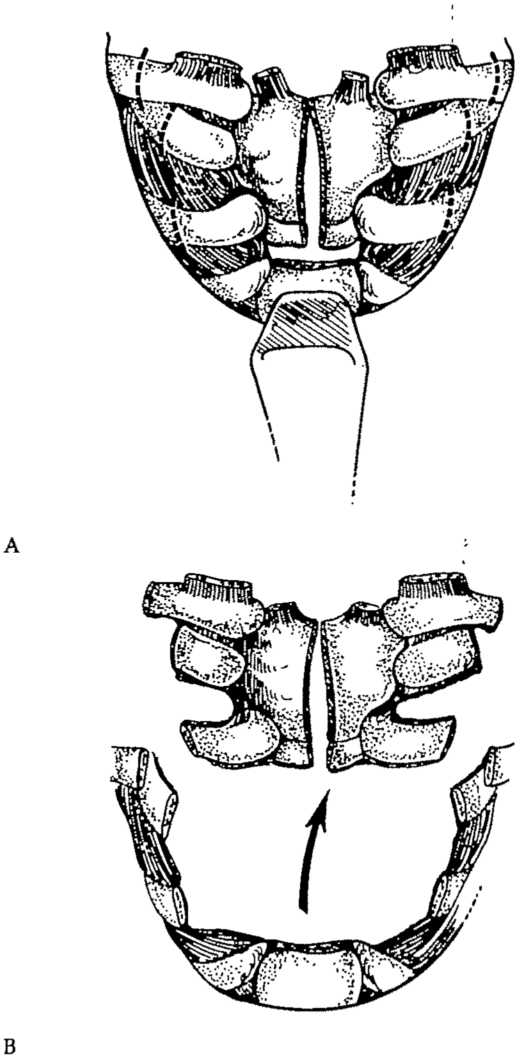

Fig 3. Once the need for mediastinal tracheostomy is known, the removal of a plate of sternum, clavicles, and first and second ribs facilitates resection and allows the bipedicled skin flap to reach the trachea easily.

In patients in whom the thyroid is not involved by tumor and in whom there will be no compromise in completeness of resection, one or both lobes of the thyroid may be left intact by dividing them in the midline and turning one or both laterally with blood supply still attached. This also preserves the parathyroid glands.

Where it is clear that the tracheostomy will lie in mediastinum, a plaque of anterior chest wall is removed at this point before the trachea is divided (Fig 3B). If on the other hand some question exists regarding the possibility of excising the lesion, the midtrachea is dissected further before the plaque of bone is removed, through the exposure provided by the divided sternum.

To remove the bony plaque to provide for the mediastinal tracheostomy, each of the clavicles is divided approximately 4 cm from its medial end by passing instruments carefully beneath the clavicle, avoiding injury to the underlying subclavian vein and dividing the bone on each side with a Gigli saw. The surgeon divides the first and second cartilages on both sides after first freeing the intercostal muscle from the junction of sternum and ribs. The plaque of clavicle, cartilage, and sternum is removed on both sides (Fig 3B). The maneuver is greatly facilitated by previous division of the sternum as described. Ideally, the pleura will remain intact.

The level of transection of the trachea is next selected, establishing an adequate margin below the level of the tumor. Particularly in thyroid carcinoma, the lymph nodes in the V of the innominate artery and left carotid artery should be dissected with the specimen. In such patients the strap muscles are usually included with the specimen. It is usually not of any help to divide the innominate veins, although tumor that invades one or another of these veins must be resected. Lateral traction sutures are placed on both sides of the distal trachea, below the level of transection, the division is made, and intubation is carried out into the distal trachea, across the operative field. The level of esophageal division is now selected. It is not always necessary to resect the esophagus completely. A narrowed esophagus left in place will serve as an excellent conduit for saliva and nutrition. Indeed, one such patient did not require dilation; the esophagus later widened with swallowing of food. If the esophagus and upper pharynx are to be removed, the esophagus can be transected distally and the entire specimen can be elevated from the prevertebral fascia.

The esophagus is usually divided with a stapler well below the lesion and then inverted with interrupted silk sutures. If the stomach is to be used for eventual reconstruction of the esophagus, the residual esophagus is removed by dissection from above through the exposed mediastinum and from below through the esophageal hiatus. In most of these patients, we preferred to use colon esophageal reconstruction and therefore turned in the esophagus at this point.

When the specimen has been elevated up to the pharynx and larynx, transection is carried out proximally. The suprahyoid musculature is divided with cautery, the superior cornua of the hyoid bone is divided sharply, and the muscles attaching to the larynx are divided in the usual manner with the superior laryngeal nerves and vessels and the specimen extracted. A substernal tunnel is made with the hand from above and below pushing more to the left than the right to avoid entering the right pleura. Meanwhile, the abdominal team has provided an adequate colon bypass. We usually use the left colon pedicled on the left colic artery; we used the right colon in only 1 patient in this series. The vascular pedicle is brought up behind the stomach, and the distal end of the colon is anastomosed to the anterior wall of the stomach. Because the vagus nerves have been divided, pyloromyotomy or pyloroplasty is added. A draining gastrostomy is placed for ease of postoperative management and a feeding jejunostomy is placed for security.

The proximal end of the colon or stomach is anastomosed to the pharynx using two layers of 4-0 interrupted silk sutures (Figs 4 and 5). This is done with meticulous care to avoid any possibilities of leakage. Even in patients who have had prior irradiation, healing can generally be counted on because the colon has not been irradiated. In addition, a pedicled omental flap brought up substernally

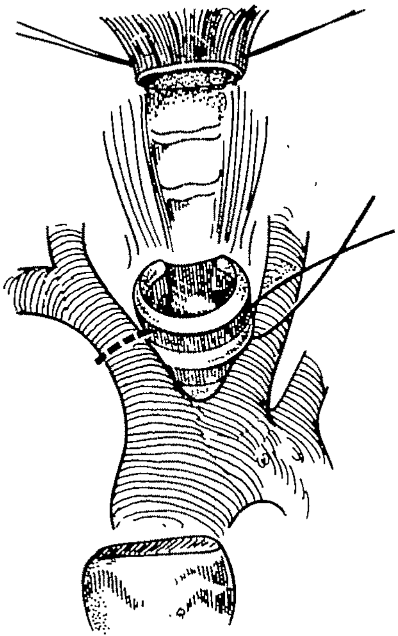

Fig 4. If it appears that pressure on the innominate artery exists, it is divided after trial occlusion under electroencephalographic control.

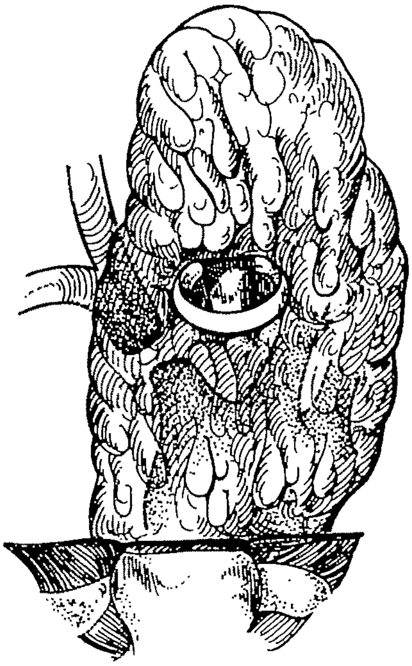

Fig 6. The omentum is used to bury the divided ends of the innominate artery and buttress the esophageal anastomosis and trachea.

is placed over the anastomosis (Fig 6). The omental pedicle is prepared by separating it from the colon and stomach, leaving the right gastroepiploic artery as its blood supply. In patients with a long omentum, the surgeon need only turn the omentum upward.

To construct a mediastinal tracheostomy, a second transverse incision is now made, usually in the submammary line from anterior axillary line to anterior axillary line (Fig 1). With the previous upper transverse incision, a large bipedicled flap is now elevated from the pectoral fascia, with great care taken to spare the lateral feeding blood vessels. The large well-vascularized flap will drop into the mediastinal defect created by removal of the sternal plaque. If it appears that the stoma will reside immediately adjacent to the innominate artery with any degree of tension, elective division of the innominate artery is performed (see Fig 4). Initially the artery is clamped and the electroencephalogram is observed. If after some time no change is observed in the electroencephalogram (assuming also that the arteries were normal on the preoperative angiogram), the artery is divided and oversewn proximally and distally with a double layer of running vascular sutures. The ends of the artery are carefully buried in healthy tissue, usually the omentum which has been brought up substernally and placed over the innominate artery and over the aortic arch to interpose the fatty tissue between the tracheal stoma and the vascular structures (see Fig 6). Even if the artery is not divided, the omentum is now usually interposed for security.

A short transverse incision is made in or a very small transverse oval is excised from the middle of the skin flap at an appropriate spot corresponding to the end of the trachea in the mediastinum. Anastomosis is made of the end of the trachea to the opening in the skin. The traction sutures are used to draw the tracheal end through the opening. Four to six absorbable sutures are placed from the subcutaneous tissues to the tracheal walls distal to the transected end and tied (Fig 7). The skin is anastomosed to the trachea margin with 4-0 Vicryl interrupted sutures (Fig 8). This may be done by intermittent removal and replacement of the endotracheal tube. After this anasto-

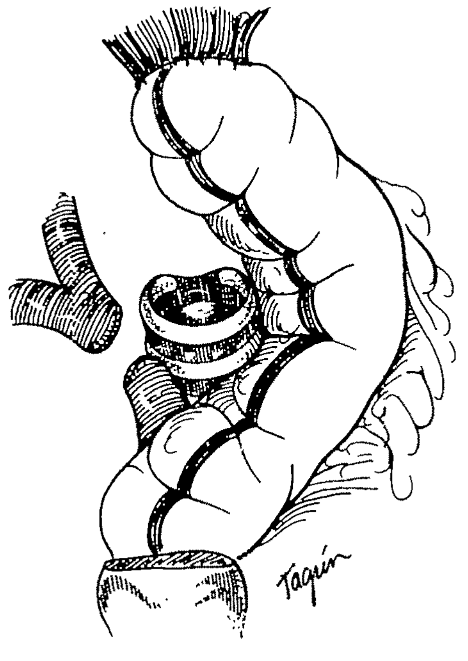

Fig 5. The anastomosis between the colon and pharynx is completed.

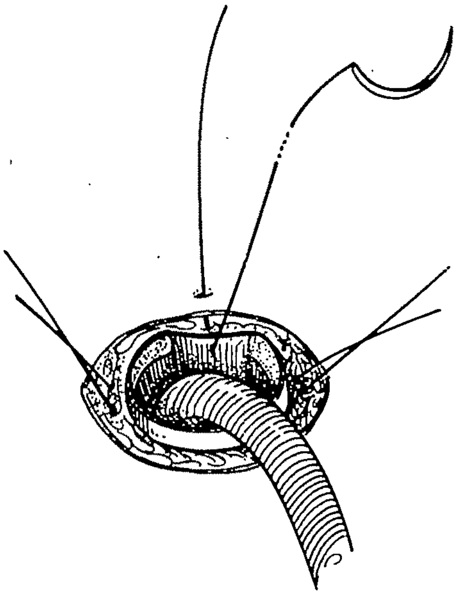

Fig 7. Sutures are placed between the subcutaneous tissues and the side of the trachea to reduce tension on the tracheocutaneous anastomosis.

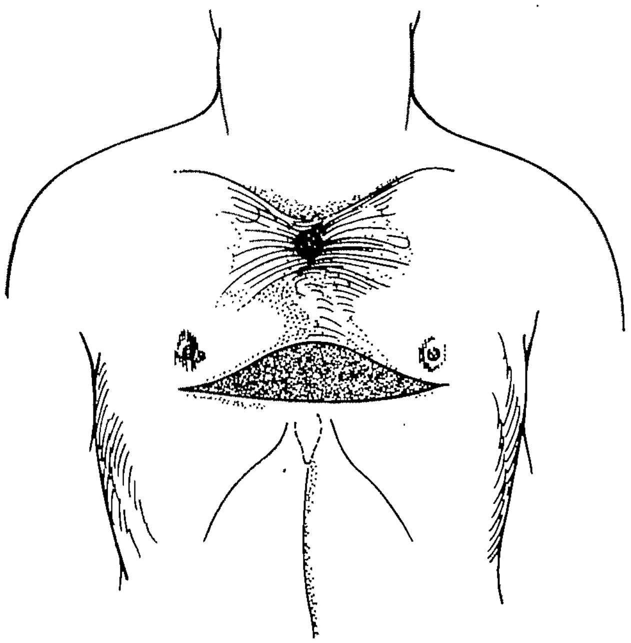

Fig 9. Completed cervical exenteration and mediastinal tracheostomy.

mosis is completed, vacuum drains are placed beneath the flaps and in the neck and mediastinum, and the upper incision is closed. Although with further mobilization of the interior margin of the inferior margin of the inferior incision it would be possible in most cases to pull the skin together, this is avoided so that tension is not placed on the tracheal cutaneous anastomosis. Therefore, the roughly elliptical defect beneath the lower incision that overlies solid chest wall and not the mediastinal defect is usually skin grafted (Fig 9).

Postoperative Care

Ventilation in patients who require it is usually provided through the inlying Tovell tube, which is carefully taped in position. Because of the anatomical disposition of the mediastinal tracheostomy, no standard tracheostomy tube will be satisfactory. As little pressure as possible is used in the cuff to avoid injury to the stomal suture line. The greatest problem in the past in mediastinal tracheostomies has been separation of the tracheostomy, with subsequent erosion and massive hemorrhage from the innominate artery or the aortic arch. With the addition of innominate artery division and placement of the omentum over the vessels, the complication of major hemorrhage has not occurred. When separation has occurred (a hazard partricularly when the patient has had preoperative irradiation), subsequent healing has occurred without hemorrhagic problems. In some of these patients with cutaneous tumor and extensive radiation change, the procedure was modified to include island myocutaneous flaps. Such problems must be foreseen and reviewed in advance with a consultant in plastic surgery. Routine use of myocutaneous flaps is not necessary to accomplish these procedures, however.

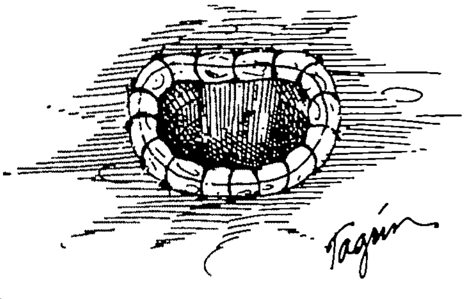

Fig 8. The tracheocutaneous anastomosis is performed with absorbable sutures.

If total thyroidectomy and parathyroidectomy has been performed, the patient will require replacement therapy. If the stoma does not heal or tends to stenosis, it may be kept open easily by using a cut-down and carefully sanded proximal end of a Hood silicone salivary tube. A laryngectomy tube is useful occasionally.

A bib is used to assist in humidification. Some of these patients have been able to learn a form of "esophageal" speech despite the colonic or gastric replacement. Others have learned preferentially to use electronic voice equipment.

Results

Eighteen patients (13 men and 5 women) ranging in age from 40 to 77 years underwent cervical exenteration. Five patients had failed previous operations and 11 had had preoperative irradiation between 5,000 and 6,000 rads. Diagnoses were carcinoma of the cervical esophagus in 7 patients, carcinoma of the thyroid in 4, adenoid cystic carcinoma of the trachea in 3, recurrent laryngeal cancer in 2, and complications of high-dose irradiation therapy in 2. The average length of hospital stay was 34.2 days (median, 38 days; range, 15 to 58 days).

Fourteen patients required resection of a plate of chest wall. A bipedicled skin flap was used to create the mediastinal tracheocutaneous anastomosis. The innominate artery was electively divided in 7 patients. This was always done under electroencephalographic monitoring. Colon bypass was used as an esophageal substitute in 10 patients. Three patients had a "gastric pull-up," and in 1 a gastric tube was reversed (the only death). Tumor invaded the muscular layer of the esophagus in 4 patients but spared the mucosa. In these patients, the muscular layer was resected, leaving the mucosa. The mucosa was left intact in 2 patients and was closed in 2. Buttressing was provided with available muscle, omentum, or vein patch. Eleven patients had omentum used to buttress the esophageal anastomosis and cover the ends of the innominate artery and to separate the artery from the tracheal stoma. Thyroid replacement, vitamin D, and calcium were required in 11 patients.

Morbidity

Ten patients experienced no major complications. Two esophageal leaks were managed successfully by drainage. One occurred in a patient who had an esophagoplasty covered with an external jugular vein patch—not a suitable covering. An anastomotic leak occurred in a patient who had a right colon bypass with esophagoterminal ileum anastomosis. Blood supply of the right colon is less dependable than that of the left [2]. Tracheal stomal separation occurred in 2 patients. One was managed conservatively by debridement, and the complication eventually resolved, with stomal stenosis requiring later revision. The second patient had separation, and a mediastinal sinus tract developed, requiring rotation of a pectoral muscle flap to fill the sinus tract successfully and cover the right carotid artery. Right-sided hemiplegia occurred in 1 patient two days postoperatively after resection of the bifurcation of the innominate artery into subclavian and carotid artery. This was successfully managed by a bypass graft of the left subclavian to the right common carotid artery. Revision of the substernal tunnel was required in 1 patient to relieve obstruction of a substernal colon bypass. Prolonged mechanical ventilation was required in 4 patients. Three of these patients had pneumonia. One iliofemoral venous thrombosis occurred. Sternal debridement was needed for exposed sternum in 1 patient.

Mortality

There was one operative death. In a reversed gastric tube used for esophageal replacement ischemic necrosis resulted in mediastinal sepsis and death.

Functional Results

Palliation of esophageal and tracheal obstruction was achieved in all patients. All patients surviving operation ultimately achieved the ability to aliment themselves orally. Esophageal dilation was required in 6 patients and was successful in all. Tracheal stomal revision was needed in 5 patients to maintain an adequate stoma. A stomal appliance was used in the early postoperative period to maintain the stomal opening.

Survival

Survival was disease dependent. One patient with postcricoidal carcinoma of the esophagus is alive 8 years after operation with no evidence of disease. The average survival of the other esophageal cancer patients was 10 months. One patient with a squamous carcinoma of the thyroid is alive 4 years after operation without evidence of disease. The other 3 patients with thyroid cancer survived between 23 and 44 months. The 2 patients with laryngeal cancer survived 5 and 23 months. Both patients who had resection for complications of radiation therapy are alive. The three patients with adnoid cystic carcinoma survived 49, 118, and 120 months.

Comment

Radical operation for malignant disease is justifiable if the risks of operation are low and if no other alternative treatments offer equivalent chance for cure. Radical operation for "benign disease" must have low morbidity and mortality and offer tremendous palliation over other alternatives. Cervical exenteration is indeed a radical operation. Careful patient selection, preoperative evaluation, and attention to technical detail allow this operation to be performed safely.

Attention to technical details can markedly diminish the risk of major complications that result in death from this type of operation. Previously, operations of this type were associated with a high incidence of fatal hemorrhage from either pressure necrosis from the trachea on the innominate artery or stomal separation and exposure of the great vessels. Technical modifications are responsible for elimination of this problem in this small series [3]. The need to resect more than a third of the trachea may require mediastinal tracheostomy and result in excessive pressure on the innominate artery. We have electively divided the innominate artery to avoid the risk of pressure necrosis. When mediastinal tracheostomy is anticipated, aortic arch angiograms should be performed to identify vascular disease in the cranial vessels that might preclude safe division of the artery. The innominate artery should be occluded for a ten-minute trial with electroencephalographic monitoring before being divided. Major changes in the electroencephalogram will preclude division. The only patient who had any neurological complications related to division of major arteries underwent resection of the bifurcation of the innominate artery into the subclavian and carotid arteries. This procedure is different from division of the innominate artery alone leaving the right subclavian and right common carotid artery intact. Moreover, no patients had suffered ischemic problems in the right arm related to division of the innominate artery.

When the artery cannot be divided, the trachea can be moved to the right of the innominate artery as originally described by Waddell and Cannon [4] and more recently by Orringer [5]. This maneuver is not suitable if less than 5 cm of distal trachea is available, as was the case in many of our patients. Also, mobilization of the trachea for such a transposition might lead to some loss of blood supply. Division of the innominate artery, resection of the chest plate, and use of the bipedicled skin flap allow less than 5 cm of distal trachea to be used in certain circumstances. All patients in our series who had less than 5 cm of distal trachea required division of the innominate artery to bring the skin flap to the trachea.

Interposition of the omentum, we believe, has been critical in eliminating problems of erosion of the great vessels. We routinely use it to separate the trachea and great vessels and cover the divided ends of the innominate artery. The omentum can be mobilized to provide sufficient length to reach the neck easily [6]. The omentum also supplies much-needed blood supply and connective tissue proliferation in patients who have had preoperative irradiation therapy. It serves to buttress esophageal closures or anastomoses between pharynx and stomach or colon.

Stomal separation usually occurs from excessive tension at the tracheocutaneous anastomosis and is more likely to occur in irradiated patients. Stomal separation in the past has led to exposure of the great vessels and subsequent fatal hemorrhage. Removal of a bony plaque has allowed the well-vascularized bipedicled skin flap to reach even the most distal mediastinal tracheostomy easily. The tracheocutaneous anastomosis can be performed without serious tension, reducing the risk of stomal separation. This relatively simple and effective flap makes use of myocutaneous flaps unnecessary except when extensive cutaneous resection is occasioned by tumor or irradiation ulceration. Three patients who suffered either stomal separation or a small fistulous tract had granulating omentum rather than bared arteries. Previously, these patients would have been at great risk for fatal hemorrhage from erosion of the innominate artery or aortic arch.

The choice of esophageal replacement is very important. Colon, stomach, free jejunal grafts, myocutaneous flaps, and reversed gastric tubes have been used [7–20]. We have had an excellent experience with left colon bypass based on the ascending branch of the left colic artery and prefer it for most patients [2]. Preoperative mesenteric arteriograms have been invaluable in assessing adequate arterial blood supply and vascular anomalies. Because the distance from the stomach to pharynx is great, proximal colonic division is performed at the hepatic flexure. The proximally divided middle colic artery serves as an arcade of blood supply in its branches. The stomach is an excellent alternative provided that sufficient length exists to reach the pharynx. The additional length obtained by dividing the left colon at the hepatic flexure is the primary advantage of colon over stomach. Use of a second surgical team to prepare the esophageal substitute dramatically reduces operating time.

These operations represent formidable challenges for the patient and physician. They may involve 12 hours or more of operation. They usually are performed in elderly patients who are at increased risk for complications either because of previous operations or high-dose irradiation therapy. Hence, such operations are best performed in centers with experience in dealing with problems of this magnitude. Postoperative care requires dedicated effort on the part of nurses, residents, and attending staff. Hospitalization is prolonged. Despite our best efforts, some patients suffered serious complications, which fortunately were effectively managed in most cases.

Justification for such an operation is that the patients are often in desperate straits, with malignancies obstructing esophagus and airway. Few alternatives exist beyond heroic operation because achieving satisfactory palliation with tubes or tracheostomies is frequently impossible. We do not believe that probability of survival less than 6 months warrants an operation of this magnitude because a substantial portion of time will be spent recovering from the operation; survival greater than 6 months, however, justifies this type of operation because of the superior palliation that can be achieved. The functional equivalent obtained is that of a laryngectomy. These patients are able to breathe, handle their saliva, and aliment themselves without need of tubes or bags. Most of our patients either learned esophageal speech or used an electrolarynx.

Long-term survival is achievable in certain diseases. Radical operation may be the only hope these patients have for long-term survival and potential cure. One of our patients with postcricoidal cervical esophageal cancer has been disease-free for 8 years, 2 patients with adenoid cystic carcinoma have survived between 5 and 10 years without disease, and 1 patient with squamous carcinoma of the thyroid has survived more than 4 years. The number of patients in this series operated on for stomal recurrence of laryngeal carcinoma is small because results of radical excision in those cases are extremely discouraging [21, 22].

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DISCUSSION

DR MARK B. ORRINGER (Ann Arbor, MI): Drs Grillo and Mathisen are to be congratulated on their management of these challenging patients requiring cervical exenteration.

A successful outcome requires use of techniques not only of the thoracic surgeon but also of the plastic surgeon, the otolaryngologist, and the endocrine surgeon.

I agree completely with Grillo and Mathisen that with careful patient selection and attention to detail, gratifying palliation and occasional long-term survival can be achieved. There are, however, a number of substantial differences in our respective operative approaches to patients requiring cervical exenteration.

The bipedicled apron flap for mediastinal tracheostomy, shown so nicely in their figures, usually is unnecessary in these patients. With a little extra downward traction on this extended cervical incision, the anterior breast plate can usually be resected through the collar incision alone, eliminating skin flaps, the need for split-thickness skin grafts, and most healing problems between the trachea and the skin.

We also use the technique of anterior mediastinal tracheostomy liberally and have done so in 69% of our 42 patients. We do not routinely obtain preoperative angiograms, however, because we are unwilling to divide the innominate artery and accept the attendent morbidity except in the most dire circumstances.

When the divided trachea is angled forward for construction of the mediastinal tracheostomy, if there is the least bit of pressure against the innominate artery, transposition of the trachea to the right and inferior to the vessel provides several more centimeters of tracheal length and a tension-free anastomosis to the skin, thereby eliminating the hazards of a tracheoinnominate artery fistula and the need to divide the innominate artery or to transpose rotated muscle or omentum. In our 42 patients, we have had only one innominate artery erosion before using such tracheal transposition.

Another point of controversy is the choice of the organ with which to restore alimentary continuity after cervical exenteration: colon, as Grillo and Mathisen prefer, or stomach. We have used the stomach in 93% of our patients, thereby avoiding the need for preoperative intestinal angiography and the added technical problem with colon. Although this is technically easier, however, the long reach required of the stomach increases anastomotic ischemia, and leak is therefore more common. Perhaps use of the omental flap, as Grillo and Mathisen have described, will help eliminate this problem. Leak is therefore more common in our group and may contribute to the increased mortality that we have had.

Finally, iatrogenic hypoparathyroidism can pose a very difficult postoperative management problem, and therefore, we should make every effort to identify and reimplant some parathyroid tissue in these patients.

I have four questions. First, is it not preferable to transpose the divided trachea beneath the innominate artery rather than resect the vessel? Second, has use of the gastric pull-up been intentionally avoided in favor of colon? Third, has an effort been made to identify and reimplant the parathyroid glands to avoid iatrogenic hypoparathyroidism? Finally, when the anterior cervical skin is involved by tumor, what flaps are used instead of the standard bipedicled flap for reconstruction of the anterior cervical skin?

DR MATHISEN: Cervical exenteration or mediastinal tracheostomy has had a long and somewhat colorful history—usually colored bright red by the fatal hemorrhage from either the innominate artery or aortic arch. The current technique that we have described represents an evolution in thinking—primarily Dr Grillo's—over many years that is aimed primarily at trying to eliminate fatal hemorrhage.

The reason that we have used the bipedicled flap in the manner we described is that it contributes to reducing tension on the tracheocutaneous anastomosis.

In terms of transposition of the trachea to the right of the innominate artery, this was first described in our institution by Wadell and Cannon many years ago and has proved somewhat awkward to use. It indeed does have a role to play, and I believe it would be useful in patients who have preexisting vascular disease or when the artery is clamped or when substantial changes in the electroencephalogram are evident. When it was used, we also added the omentum to buttress between it and the trachea because the pressure can occur anteriorly or posteriorly; we believe that even when the trachea has been transposed, there is a potential for pressure on the vessel posteriorly.

The ability to transpose the trachea presumes that it is of sufficient length to allow transposition. Many of our patients had less than 5 cm of distal trachea available; therefore, it would have been unsuitable for transposition in this fashion.

Finally, mobilization of the trachea, as Dr Orringer described, may jeopardize the blood supply. We have had very good results with division of the innominate artery in the fashion that we have described. We have had no neurological complications or patients with right arm ischemia from doing this.

In terms of the point about using the stomach versus the colon, I think it is a matter of the surgeon's choice in some respect. Our institution has had a long and favorable experience, thanks to Dr Earl Wilkins, with colon bypass. I think our familiarity with performing colon bypass and the ability to gain all of the necessary length when the middle colic artery is included and the division of the colon takes place at the hepatic flexure has prompted us to use this technique. I certainly have no objection to using the stomach and I believe its use shortens operating time slightly. It requires one less anastomosis, and as long as it reaches the pharynx, it is a suitable alternative.

The point about parathyroids I think is well taken. I apologize for not stressing that myself. Attempts are made to identify parathyroids and reimplant them whenever possible. Often in many of these large, bulky tumors, especially the ones involving the thyroid, the parathyroid is impossible to find but, if identified, should be implanted in the hope of avoiding the problems with hypoparathyroidism that may develop.

In patients in whom irradiation or tumor has destroyed the cervical skin, we usually have plastic surgeons use myocutaneous flaps and rotate them to cover the defect. I believe that one must be flexible in dealing with these complicated problems and be able to adopt to the unique circumstances presented by each patient.

DR GRILLO: If some of you were surprised by the small number of recurrent laryngeal cancers of the stoma, that was deliberate.

We have been asked to examine many of these patients over the years, but as is evident from the work of Sisson and others who have used this type of radical resection, recurrence is almost uniform and in most cases quite prompt, as in our patients. That probably has to do with permeation of lymphatics. We have therefore operated on such patients only under very special circumstances.

Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 3, 1991. The closing date for registration is August 1, 1990.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Hospital Death on a Cardiac Surgical Service: Negative Influence of Changing Practice Patterns

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From January 1982 through December 1985, 3,772 patients underwent a cardiac surgical procedure for coronary or acquired heart disease. Operative mortality increased from 4% in 1982 to 7% in 1985 ($p < 0.001$ by χ^2 analysis). There was an increase over time of patients older than 70 years ($p < 0.001$). Female patients increased from 31% in 1982 to 35% in 1985 ($p < 0.001$). The percentage of patients having isolated coronary artery bypass grafting decreased from 69% in 1983 to 60% in 1985 ($p < 0.001$), and hospital mortality after this procedure increased ($p = 0.058$). Patients requiring more complex procedures including multiple-valve operations or combined valve replacement or repair plus bypass grafting increased from 1982 through 1985 ($p = 0.005$). Reoperations for multiple-valve procedures or combined valve repair or replacement plus coronary artery bypass grafting also increased ($p = 0.02$), particularly for patients more than 70 years of age ($p < 0.001$). Changing practice patterns have had a negative impact on surgical results. This evolution in cardiac surgical practice has important implications related to peer review and quality-assurance screening, diagnosis-related group reimbursement, and reporting of surgical outcomes to governmental agencies.

(Ann Thorac Surg 1990;49:410–2)

The utilization of in-hospital mortality as the sole criterion for the assessment of quality of care provided after a cardiac surgical procedure has received widespread attention in the lay press in recent years [1]. However, when evaluating the effectiveness of care and comparing results among different institutions, multiple risk factors must be assessed to ensure that the populations at risk are comparable.

During the era of hospital reimbursement based on diagnosis-related groups and governmental oversight of hospital events to determine acceptable indicators for cardiac surgical practice, it is important to perform continuous in-house quality-assurance screening to examine changes in risk factors and surgical outcomes. The present study was performed as a response to a perceived increase in referrals of high-risk patients to our center with a tendency toward less favorable results.

For editorial comment see page 347.

Material and Methods

From January 1, 1982, through December 31, 1985, 3,772 patients underwent a cardiac surgical procedure for repair of coronary or acquired heart disease at the Deborah Heart and Lung Center. Age ranged from 21 to 89 years. There were 2,545 men (67.5%) and 1,227 women (32.5%).

Procedures performed included the following: isolated coronary artery bypass grafting in 2,390 patients (63%), valve repair or replacement plus coronary artery bypass grafting in 384 (10%), isolated aortic valve replacement in 354 (9%), isolated mitral valve replacement in 297 (8%), multiple-valve repair or replacement in 276 (7%), isolated mitral valve repair in 64 (1.7%), and isolated tricuspid valve replacement in 7 (0.2%). Two hundred ninety-eight (8%) of these patients had had at least one prior cardiac surgical procedure.

The study was carried out in a retrospective manner with a review of each patient's chart. Analysis was made of age, sex, and procedures performed to determine current practice trends and their effect on hospital survival.

The statistical methods employed to analyze the data included χ^2 analysis, the Fisher exact test, two-sample t test, and 70% confidence limits.

Results

Procedures Performed

The number of cardiac surgical procedures performed annually decreased from 997 in 1982 and 1,032 in 1983 to 898 in 1984 and 845 in 1985 ($p < 0.001$ by χ^2 analysis).

Of the 3,772 patients undergoing a cardiac operation from 1982 through 1985, 2,390 (63%) underwent isolated coronary artery bypass grafting. The percentage of patients undergoing this procedure decreased significantly from 64% of the total in 1982 and 69% in 1983 to 60% in both 1984 and 1985 ($p < 0.001$). During the same period, 206 patients underwent percutaneous transluminal coronary angioplasty (PTCA). The number of patients having

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Table 1. Percentage of Patients Undergoing More Complex Operations by Year[a,b]

Year of Operation	All Patients	No.	%	70% Confidence Limits
1982	997	252	25	24%–27%
1983	1,032	223	22	20%–23%
1984	898	254	28	27%–30%
1985	845	229	27	25%–29%
Total	3,772	958	25.4	24.6%–26%

[a] More complex operations included reoperations, multiple-valve repair or replacement, or valve replacement or repair plus coronary artery bypass grafting. [b] Significance: $p = 0.058$ by Mantel-Haenszel test for increasing incidence of more complex operations over time.

Table 2. Percentage of Patients Having Cardiac Operation at More Than 70 Years of Age by Year[a]

Year of Operation	All Patients	No.	%	70% Confidence Limits
1982	997	81	8	7%–9%
1983	1,032	96	9	8%–10%
1984	898	147	16	15%–18%
1985	845	158	19	17%–20%
Total	3,772	482	12.8	12%–13%

[a] Significance: $p < 0.001$ by χ^2 test for increasing percentage of patients 71 years old or older over time.

PTCA increased from 13 in 1982 and 13 in 1983 to 33 in 1984 and 147 in 1985 ($p < 0.001$).

Reoperations, multiple-valve repairs or replacements, and combined valve repair or replacement plus coronary artery bypass grafting procedures were performed in 958 (25%) of the 3,772 patients. The percentage of patients requiring these more complicated operations showed a tendency to increase from 1982 through 1985 (Table 1). Although the percentage of patients undergoing reoperation for isolated coronary artery bypass grafting was unchanged during the study ($p = 0.36$), the frequency of patients undergoing reoperation for multiple-valve procedures or combined valve repair or replacement plus coronary artery bypass grafting increased during the study. In the year 1982, 22% of the patients underwent reoperation for multiple-valve replacement or repair, or combined procedures; in 1983, 19%; in 1984, 30%; and in 1985, 29% ($p = 0.02$). The percentage of patients undergoing reoperation who were more than 70 years of age at the time of reoperation increased significantly during the study from 6% of the patients having reoperation in 1982 and 2% in 1983 to 24% in 1984 and 28% in 1985 ($p < 0.001$).

Demographics

The percentage of female patients undergoing a cardiac surgical procedure increased during the period of the study from 31% in 1982 and 29% in 1983 to 36% in 1984 and 35% in 1985 ($p < 0.001$).

There was important change in the age of the patients having operation in the latter years of the study. The percentage of patients who were 21 through 70 years old decreased significantly ($p < 0.001$), while the percentage of patients 71 years of age or older increased markedly (Table 2).

Hospital Death

The risk of hospital death after a cardiac surgical procedure increased during the study. Forty-two (4%) of 997 patients died in 1982, 46 (5%) of 1,032 patients died in 1983, 55 (6%) of 898 patients died in 1984, and 60 (7%) of 845 patients died in 1985 ($p < 0.001$).

There were 15 hospital deaths (4%) among the 354 patients undergoing isolated aortic valve replacement, with no effect of year of operation ($p = 0.33$). Thirteen (4%) of 297 patients having isolated mitral valve replacement died, again with no effect of year of operation ($p = 0.67$). Hospital death occurred in 43 (11%) of 384 patients having combined valve procedure and coronary artery bypass grafting, with no difference according to year of operation ($p = 0.29$).

There was a significant increase in hospital death during latter years of the study for patients undergoing isolated coronary artery bypass grafting (Table 3). Thirty-two (12%) of 276 patients who had multiple valves repaired or replaced died, and there was a tendency toward an increased risk with more recent year of operation ($p = 0.079$).

There were 40 deaths (13%) among 298 patients undergoing reoperation, with no effect of year of operation ($p = 0.96$). Forty-eight of the 298 patients were more than 70 years of age, and 42 of these older patients were seen in the last 2 years of the study ($p < 0.001$). There was a decrease in the risk of hospital death in these elderly patients undergoing reoperation during the years 1984 and 1985 ($p = 0.0002$).

Comment

Public disclosure of operation-related in-hospital mortality has gained widespread acceptance [2]. The use of this single variable to assess effectiveness of care, although commonplace, is inadequate. Improvements in preoperative preparation, intraoperative techniques of myocardial preservation, and postoperative care have had a positive impact on perioperative mortality over the last two dec-

Table 3. Hospital Death Among Patients Having Coronary Artery Bypass Grafting by Year[a]

Year of Operation	No. of Patients	No. of Deaths	%	70% Confidence Limits
1982	639	15	2	1.7%–3%
1983	711	27	4	3%–5%
1984	536	24	5	3.6%–6%
1985	504	27	5	4%–7%
Total	2,390	93	3.9	3%–4%

[a] Significance: $p = 0.058$ by χ^2 test for increasing hospital death among this category of patient over time.

ades [3, 4]. This review was performed to examine the perception that the type of cardiac surgical referrals to our institution had led to a more complex practice during the study period.

The increase in hospital deaths noted during the study appeared to be related to changing referral and demographic patterns, with an increase in the complexity of operations performed. For example, the initial results of the multicenter Coronary Artery Surgery Study favored medical rather than surgical treatment in many cohorts of patients with coronary artery disease [5]. This management protocol had a large crossover from medical management to surgical intervention. Patients in whom medical management has failed may be older with more advanced disease when they enter surgical management [6].

Similarly, PTCA has altered our practice in several ways. The effect of PTCA can be short-lived, thus necessitating surgical intervention in as many as 33% of patients who initially had successful angioplasty [7]. Also, PTCA has introduced a subpopulation of patients who previously would have been candidates for an elective surgical procedure but who instead represent failures of emergent PTCA. Several studies [8, 9] have reported a higher mortality in these patients.

The percentage of patients requiring reoperation, multiple-valve procedures, or a combination of valve procedures and coronary artery bypass grafting increased during the study period. There was an important increase in the percentage of elderly patients having operation, and more complex procedures in the elderly were performed. While the age of the population at risk is increasing, our indications are becoming more liberal [10, 11]. As the field of cardiac surgery has matured, more patients are at risk for reoperation as a result of prosthetic valve malfunction or degeneration and for coronary artery bypass grafts to become diseased and fail.

The percentage of female patients having operation has recently increased. The rate of coronary artery disease in women has increased secondary to the postulated effect of the greater population of female smokers and female executives in high-stress positions [12].

Tertiary care centers are seeing patients with more complex conditions who are at higher risk [13, 14]. This may be good medical practice but can have a negative impact on the reputation of the tertiary referral center. Furthermore, the introduction of a compensation system based on diagnosis-related groups, with severe limitations on reimbursement related to hospital stay, has influenced the health care delivery to these patients [15].

All of these factors tend to alter the demographics of the patient population. The result has been an increase in the hospital death rate during the study with a 75% increase in mortality over the 4-year period. The effectiveness of care has remained unchanged; only the disease has changed.

In conclusion, there has been an increase in hospital mortality after cardiac surgical procedures, an increase related to altered cardiac surgical practice patterns in our center. Clinical risk adjustment must be utilized to allow patients, legislators, and physicians to better assess the effectiveness of health care delivery.

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Clinical Trial of Nicardipine Cardioplegia in Pediatric Cardiac Surgery

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To clarify the effectiveness of nicardipine, one of the dihydropyridine calcium-channel blockers, for myocardial protection during cold potassium cardioplegic arrest in pediatric cardiac surgery, a clinical trial of nicardipine (0.25 mg/L) added to potassium cardioplegic solution was performed in children undergoing surgical repair of congenital heart diseases. Twenty patients were selected to receive nicardipine cardioplegia and 13 patients received a standard potassium cardioplegia, serving as a control group. Nicardipine cardioplegia provided better cardiac performance in the early postoperative period and reduced release of the MB isozyme of creatine kinase, as determined during a 48-hour postoperative period. These results suggest that nicardipine added to cold potassium cardioplegic solution offers additional protection for the myocardium during ischemia and postischemic reperfusion in pediatric cardiac surgery.

(Ann Thorac Surg 1990;49:413–8)

For the last decade, cold potassium cardioplegia has been widely accepted as protecting the ischemic myocardium during cardiac operations. This cardioplegia is not optimal, however, and further improvement of myocardial protection is needed. More recently, slow-calcium-channel blockers have been suggested to provide additional protection when included in cardioplegic solutions used during aortic cross-clamping [1–5]. Slow-calcium-channel blockers, which inhibit the influx of calcium ions into myocardial cells by blockade of the slow channel, provide myocardial electrical arrest and are potent coronary vasodilators. In addition, slow-calcium-channel blockers may provide a cytoprotective effect by inhibiting calcium overload in the ischemic myocardium.

Use of calcium-channel blockers is still controversial, however. Recent reports [6] have suggested that calcium-channel blockers failed to afford any additional protection because of a temperature dependency for the effectiveness of these agents when used under the clinically relevant condition of hypothermic ischemic arrest in cardiac surgery. Furthermore, little is known regarding clinical use of calcium antagonists for intraoperative myocardial protection in children with congenital heart disease. The present study was designed to evaluate the efficacy of nicardipine, one of the dihydropyridine calcium-channel blockers, for myocardial protection during hypothermic cardioplegic arrest in pediatric cardiac surgery.

Material and Methods

Thirty-three patients aged less than 10 years underwent repair of a variety of types of congenital heart disease at Yamaguchi University Hospital from September 1986 to May 1987. Patients were randomly assigned by hospital number to one of two groups. Twenty patients received nicardipine in cardioplegic solution and 13 patients received our standard cardioplegic solution as a control group. The study protocol was approved by the institutional human research committee at Yamaguchi University Hospital. Type of operation and number of patients are shown in Table 1. On the whole, there were no differences in the severity and complexity of disease between the two patient groups.

Operative Technique

After performance of a median sternotomy, the aorta was cannulated at the ascending aorta, and the superior and inferior venae cavae were cannulated through the right atrium. Cardiopulmonary bypass was established with a standard bubble oxygenator and roller pump at flows of 2.0 to 2.5 L/min/m^2. Hypothermic perfusion was used to cool the patients to 25°C or less. In all patients, myocardial protection during aortic cross-clamping was assured by the combination of cold potassium cardioplegia and topical cooling of the heart with ice-cold saline solution. The composition of the cardioplegic solution was as follows: Na, 25.2 mEq/L; K, 23.0 mEq/L; Mg, 5.0 mEq/L; Cl, 26.6 mEq/L; glucose, 48.1 g/L; Tris buffer, 3.0 mM; pH (37°C), 7.4; osmolarity, 345 mosm. The cardioplegic solution was infused into the aortic root at an initial volume of 15 mL/kg of body weight, and an additional 10 mL/kg of cardioplegic solution was infused every 20 minutes during aortic clamping. The patients in the nicardipine group received cardioplegic solution containing 0.25 mg/L of nicardipine (Fig 1).

Postoperative Care

After termination of cardiopulmonary bypass, a Swan-Ganz catheter was inserted into the pulmonary artery to determine cardiac output postoperatively by thermodilution method, using in each instance the means of triplicate measurements. During the first 24 hours after operation,

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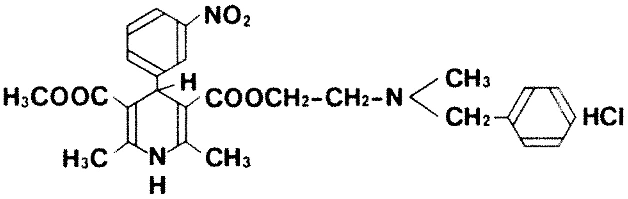
Table 1. Profile of Operations and Number of Patients

Operations	Control Group	Nicardipine Group
Atrial septal defect	3	1
Ventricular septal defect	6	10
Pulmonary stenosis	2	2
Endocardial cushion defect	1	3
Tetralogy of Fallot	1	3
Fontan operation	0	1
Total	13	20

intravenous fluid was restricted to 750 $mL/m^2/24$ h and blood, plasma, or both was transfused to maintain hemodynamic stability and hematocrit at approximately 35%. Arterial pressure, central venous pressure, and pulmonary arterial pressure were monitored continuously during the early postoperative period. Twelve patients required inotropic support with 5 to 15 μg/kg/min of dopamine or dobutamine, and 3 of them required combined use of vasodilators. As an indicator of myocardial injury during operation, serial changes in serum activity of the MB isoenzyme of creatine kinase (CK-MB) were measured for 48 hours after termination of cardiopulmonary bypass. Creatine kinase activity was determined by a spectrophotometric kinetic method, and the isozymes were separated according to the electrophoresis technique. The total amount of CK-MB release was calculated by the following formula [7]: Total CK-MB release (IU/L) $= E(T) + kd\int E(t)dt$, where total CK-MB release = cumulative activity of CK-MB released by heart up to time T, $E(t)$ = activity of CK-MB in serum (IU/L) at time t, and kd = the fractional rate of disappearance of CK-MB from blood.

Statistical Analysis

Statistical analyses of time-related data were performed by two-way analysis of variance. Other data were analyzed by Student's *t* test or χ^2 test where appropriate. Probability values less than 0.05 were considered statistically significant. Data are expressed as mean ± standard deviation of the mean.



$C_{26}H_{29}N_3O_6 \cdot HCl$ = 516.0

2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylic acid 3-[2-(N-benzyl-N-methylamino)]-ethyl ester 5-methyl ester hydrochloride

Fig 1. Chemical structure of nicardipine.

Table 2. Variables in 33 Study Patients[a]

Variable	Control Group	Nicardipine Group	*p* Value
Age (yr)	4.4 ± 3.0	4.8 ± 3.3	NS
Total bypass time (min)	68 ± 23	84 ± 33	NS
Aortic cross-clamp time (min)	40 ± 17	49 ± 23	NS
Temperatures (°C)			
Esophageal	23 ± 3	22 ± 4	NS
Rectal	27 ± 3	26 ± 3	NS
Spontaneous defibrillation (%)	53.8 (7/13)	75.0 (15/20)	NS
Inotropic support (%)	38.5 (5/13)	35.0 (7/20)	NS

[a] Data are shown as the mean ± standard deviation.

NS = not significant.

Results

There were no operative deaths, and all patients are alive and well after hospital discharge. Variables analyzed were age, total bypass time, aortic cross-clamp time, body temperatures, spontaneous defibrillation, use of inotropic agents, and early postoperative hemodynamics (Table 2). Ages ranged from 6 months to 10 years. Twelve patients were girls and 21 were boys. There were no significant differences in average age, total bypass time, aortic cross-clamp time, body temperatures, incidence of spontaneous defibrillation, or use of inotropic agents between the two groups.

Postoperative Hemodynamics

Selected hemodynamic variables at three hours after bypass are shown in Table 3. Heart rate, central venous pressure, and pulmonary capillary wedge pressure were nearly identical between the two groups. Mean arterial pressure was 70 ± 13 mm Hg in the control group and 79

Table 3. Selected Hemodynamic Variables at Three Hours After Bypass[a]

Hemodynamic Variable	Control Group	Nicardipine Group	*p* Value
Heart rate (beats/min)	121 ± 19	120 ± 17	NS
CVP (mm Hg)	9.3 ± 2.6	8.9 ± 2.9	NS
PCWP (mm Hg)	8.7 ± 3.2	7.7 ± 2.8	NS
MAP (mm Hg)	70 ± 13	79 ± 13	NS
Cardiac index ($L/min/m^2$)	2.80 ± 0.84	4.00 ± 0.89	<0.01
LVSWI ($g \cdot m/beats/m^2$)	21.5 ± 14.3	34.6 ± 15.3	<0.05
SVRI ($dynes \cdot s \cdot cm^{-5}$)	2,000 ± 671	1,566 ± 434	NS

[a] Data are shown as the mean ± standard deviation.

CVP = central venous pressure; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; NS = not significant; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index.

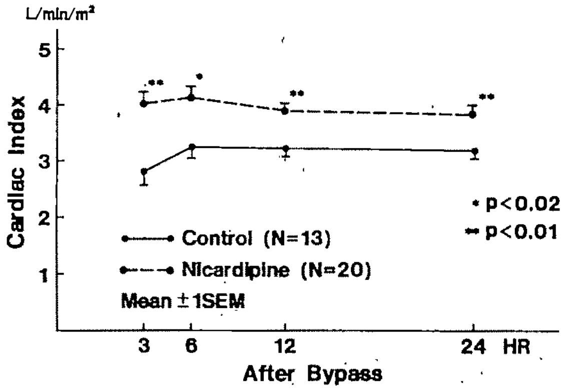


*Fig 2. Mean and standard error (SEM) of sequential cardiac index measurements in the postoperative period. Cardiac indexes in the nicardipine group were greater than those in the control group during the postoperative 24 hours (p < 0.01 by analysis of variance). (*p < 0.02 versus the control group [by t test]; **p < 0.01 versus the control group [by t test].)*

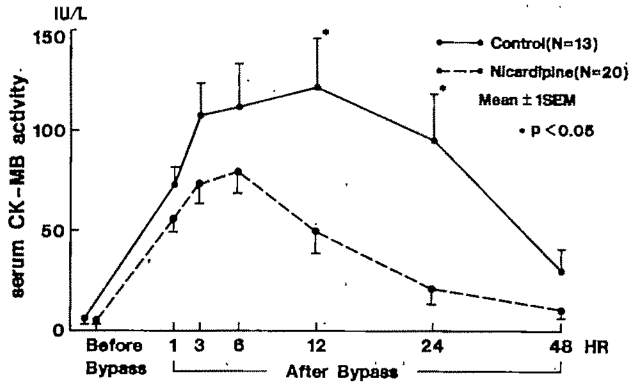


*Fig 4. Mean and standard error (SEM) of sequential serum CK-MB isozyme measurements in the postoperative period. The serum activity curve for 48 hours in the nicardipine group was significantly lower than that in the control group (p < 0.01 by analysis of variance). (*p < 0.05 versus the nicardipine group [by t test].)*

± 13 mm Hg in the nicardipine group, which was not significant. At a comparable preload and heart rate, however, the nicardipine group had a greater cardiac index (4.00 ± 0.89 versus 2.80 ± 0.84 L/min/m^2) and left ventricular stroke work index (34.6 ± 15.3 versus 21.5 ± 14.3 g · m/beats/m^2) than the control group.

The time courses of two variables, cardiac index and pulmonary capillary wedge pressure, are shown in Figures 2 and 3. Postoperative cardiac indexes were 3.28 ± 0.88 at 6 hours, 3.26 ± 0.66 at 12 hours, and 3.22 ± 0.54 L/min/m^2 at 24 hours in the control group, and 4.09 ± 0.89 at 6 hours, 3.93 ± 0.59 at 12 hours, and 3.86 ± 0.50 L/min/m^2 at 24 hours in the nicardipine group. Cardiac indexes in the nicardipine group remained significantly higher than those in the control group during the 24-hour postoperative period ($p < 0.01$ by analysis of variance). Pulmonary capillary wedge pressures were 9.1 ± 3.1 at 6 hours, 9.0 ± 2.9 at 12 hours, and 9.2 ± 3.5 mm Hg at 24 hours in the control group, and 7.7 ± 3.1 at 6 hours, 7.4 ± 2.9 at 12 hours, and 6.6 ± 3.0 mm Hg at 24 hours in the nicardipine group. Pulmonary capillary wedge pressures in the nicardipine group were significantly lower than those in the control group ($p < 0.01$ by analysis of variance). Heart rate and mean arterial pressure were statistically identical during the 24-hour study period. These data show that the nicardipine group had improved cardiac performance in the early postoperative period as compared with the control group.

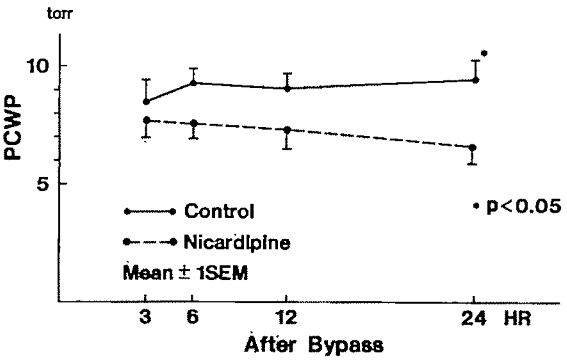


*Fig 3. Mean and standard error (SEM) of sequential pulmonary capillary wedge pressure (PCWP) measurements in the postoperative period. Pulmonary capillary wedge pressures in the nicardipine group were lower than those in the control group during the postoperative 24 hours (p < 0.01 by analysis of variance). (*p < 0.05 versus the nicardipine group [by t test].)*

Creatine Kinase MB Assays

As an indicator of myocardial ischemic injury during operation, serial changes in serum CK-MB isozyme activity were monitored for 48 hours after termination of cardiopulmonary bypass (Fig 4). In the control group, the peak in average CK-MB activity was 121 ± 97 IU/L at 12 hours after termination of cardiopulmonary bypass. In the nicardipine group, the peak activity was 78 ± 50 IU/L at six hours. The serum CK-MB activity curve for 48 hours in the nicardipine group was significantly lower than that in the control group ($p < 0.01$ by analysis of variance). For quantitative evaluation of myocardial leakage of CK-MB, the average peak CK-MB activity in individual patients and total CK-MB releases were calculated (Table 4). The total CK-MB release in the nicardipine group was significantly less than that of the control group ($p < 0.05$), indicating less myocardial damage during cardioplegic arrest.

Comment

In the last few years, numerous investigations of myocardial protection during cardiac operations have focused on

Table 4. Quantitative Evaluation of Creatine Kinase MB Fraction Release[a]

Variable	Control Group	Nicardipine Group
Peak CK-MB (IU/L)	140 ± 90	88 ± 51
Total CK-MB release (IU/L)	272 ± 183	126 ± 80[b]

[a] Data are shown as the mean ± standard deviation. [b] $p < 0.05$ as compared with the control group.

CK-MB = MB isoenzyme of creatine kinase.

calcium metabolism during ischemia and reperfusion. In 1972, Shen and Jennings [8] first proposed the hypothesis that intracellular calcium influx was the critical event in the transition from reversible to irreversible tissue damage of ischemic and reperfused myocardium. The intracellular calcium overloading produces a deterioration of mitochondrial function, which can be quantitated in terms of a reduced oxidative phosphorylating activity and an impaired adenosine triphosphate-generating capacity [9]. In the ischemic myocardium, decrease in the tissue stores of adenosine triphosphate occurs through depressed aerobic glycolysis and impairs the integrity of cell membrane and the maintenance of intracellular calcium homeostasis [10]. The excessive calcium influx leads to ischemic contracture, the "stone heart" syndrome, which is a life-threatening event.

Calcium is an essential element in the myocardial cell. It is required for integrity of cell membranes and the enzyme system and for activation of the contraction apparatus. Four pathways exist for calcium ions to enter the cell: passive diffusion, exchange with sodium, voltage-activated transport, and possibly also exchange with potassium. The calcium ions carried by these pathways to the interior of the myocardial cell generally serve as a chemical and electrical messenger. Calcium antagonists mainly inhibit entry of calcium ions during the plateau phase of the action potential and thereby exert a negative inotropic effect on the heart and cause vasodilatation in the vascular vessels [11].

The elements necessary for effective myocardial protection during cardioplegic arrest play an important role: energy sparing by rapid induction of electromechanical cardiac arrest, slowing down of energy consumption during ischemia by hypothermia, and combating of harmful changes caused by ischemia and reperfusion with protective agents. Inadequate protection may have resulted from heterogeneous cardioplegic delivery, incomplete electrical and mechanical arrest, or loss of high-energy phosphates during ischemia. In view of these considerations, calcium antagonists may offer substantial advantages in myocardial protection during surgically induced arrest.

The possible role of calcium antagonist cardioplegia appears to be that of ensuring homogeneous delivery of cardioplegic solution, profound electromechanical cardiac arrest, and preservation of high-energy phosphates through inhibition of intracellular calcium overload. Calcium antagonists are potent coronary vasodilators and have been reported to improve cardioplegic delivery in an animal model of limited coronary flow [12]. Persistent microfibrillatory electrical activity and resultant mechanical activity were reported despite apparently adequate hypothermic potassium cardioplegic arrest [13]. Calcium antagonists may augment the electrical and mechanical arrest achieved with hypothermia and potassium [1, 4]. Preventing intracellular calcium accumulation reduces adenosine triphosphate hydrolysis, improves oxidative phosphorylation during reperfusion, and promotes adenosine triphosphate restoration [10, 14]. Experimental studies [4, 5, 15] have shown that calcium antagonists preserve high-energy phosphate stores after cardioplegic arrest.

The most widely used calcium antagonists (nifedipine, verapamil, and diltiazem) have been studied to evaluate their protective effects on myocardial ischemia and reperfusion in animals. Nicardipine is a dihydropyridine calcium antagonist similar to nifedipine and is as potent a coronary vasodilator as nifedipine. Hashimoto and associates [16] showed that nicardipine limited myocardial infarct size in baboons and dogs. Possible mechanisms of beneficial effects on the ischemic myocardium reported were an increase in myocardial oxygen tension, which is caused mainly by increased regional blood flow, and some direct protective effects on ischemic myocardial cells [17]. Nicardipine has much less effect on atrioventricular conduction and myocardial contractility than do verapamil and diltiazem [16].

With regard to myocardial protection during open heart operations, many investigators [1, 3–5, 12, 15] have reported additional protective effects of calcium antagonists as adjuncts to potassium cardioplegia in anesthetized animals and isolated perfused hearts of several species. In some studies, however, calcium antagonists did not significantly ameliorate protection by hypothermic potassium cardioplegia. Most of the negative studies were done by Hearse and colleagues [6], who reported a temperature dependency for the effectiveness of calcium antagonists and merely a redundant effect of the agent under conditions of hypothermia. On the other hand, Nayler [3] showed that the protective effects of hypothermia and nifedipine are additive, and the protective effect of nifedipine was more demonstrable in an extended period of ischemia. Boe and co-workers [18] reported that nifedipine in combination with hypothermic potassium cardioplegia effectively controlled myocardial calcium sequestration during ischemia and reperfusion.

Few clinical trials of calcium antagonists added to a cardioplegic solution have been published. Clark and associates reported the first clinical experience with nifedipine cardioplegia [2] and later reported that nifedipine and cold potassium cardioplegia improved cardiac performance immediately after operation and reduced the incidence of acute low cardiac output death in a group of high-risk patients [19]. Hicks and colleagues [20] reported that verapamil in cold potassium cardioplegia and nifedipine instituted postoperatively resulted in a reduction in postoperative creatine kinase release and fatal arrhythmias. Grondin and colleagues [21] reported excellent protective effects of diltiazem as the sole arresting agent in cold crystalloid cardioplegia in patients undergoing coronary artery bypass grafting. The potential benefits of calcium antagonist cardioplegia must be balanced by the potential risks. Christakis and colleagues [22] documented that diltiazem cardioplegia may not be beneficial for patients with poor ventricular function because diltiazem was a potent negative inotrope and produced prolonged electromechanical arrest. In the present study using nicardipine cardioplegia, however, there was no deterioration in ventricular function or atrioventricular conduction in the perioperative and postoperative periods.

Age-related differences appear to exist with respect to myocardial calcium metabolism. These differences include affinity of the sarcoplasmic reticulum for calcium ion, the calcium regulatory function of the sarcolemma, the relative inotropic response to exogenous calcium, and the effect of hypoxia on calcium influx and resulting depression of contractile function [23, 24]. Boucek and associates [25] found a greater sensitivity to calcium antagonists in the immature heart. Lupinetti and co-workers [15] showed that addition of verapamil to a potassium cardioplegic solution enhanced myocardial protection in the immature canine heart after normothermic global ischemia. In our clinical trial, addition of nicardipine to a cold potassium cardioplegic solution improved immediate postoperative cardiac performance and lessened myocardial CK-MB release in children undergoing surgical repair of congenital heart diseases. A dose of 0.25 mg of nicardipine in 1 L of cardioplegic solution did not produce the disadvantageous sequelae of calcium antagonists clinically. These results suggest the usefulness of nicardipine as an adjunct to potassium cardioplegia for cardiac surgery in children.

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INVITED COMMENTARY

In this article Mori and colleagues examined the effectiveness of nicardipine as an additive to cardioplegic arrest in pediatric cardiac surgery. It was concluded that nicardipine offers additional protection for the myocardium. This conclusion was based on the observations that (1) indices of mechanical function were improved by nicardipine three to 24 hours after reperfusion and (2) reperfusion-induced elevation of serum CK-MB level was reduced by nicardipine. Is this conclusion justified? In my view it is not.

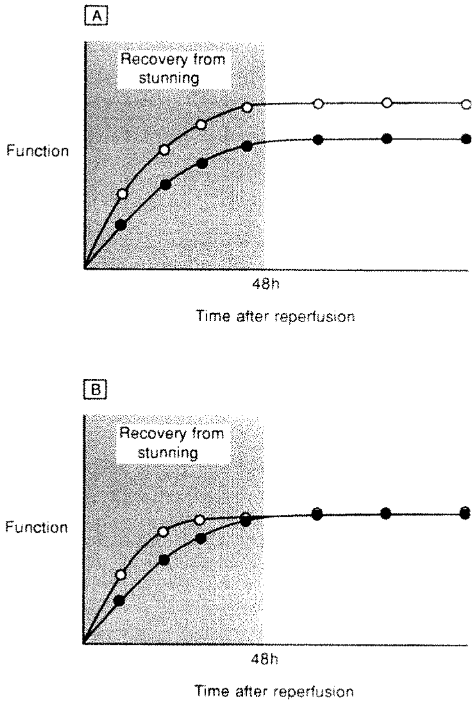

Fig 1. Hypothetical relationship between recovery of cardiac function (eg, cardiac output or slope of the Frank-Starling curve) and time after reperfusion. Filled circles *are controls and* open circles *represent an intervention group. In (A) the intervention is shown providing sustained improvement of function. In (B) the intervention is shown providing transient protection representing an action best described as a hastening of recovery from stunning. Note that comparative assessment of function at least two days after reperfusion (sufficient to allow a stable level of function to be reached) is necessary to allow distinction between these alternative effects [3]. Part (A) defines a type-A intervention as one providing additional protection to that resulting from recovery from stunning. Part (B) defines a type-B intervention as one that merely hastens recovery from stunning.*

There are two pieces of information pertaining to Mori and colleagues' data that must be emphasized. First, hemodynamic status was monitored for only 24 hours during reperfusion. Second, "all patients are alive and well after hospital discharge." It is unquestionably the case that survival and good health are ultimate arbiters of the adequacy of myocardial protection. Therefore the present study indicates that although laboratory indices of myocardial function were improved by nicardipine in the short term, the ability of the myocardium to function effectively in the long term was de facto unmodified. In view of this apparent paradox a degree of circumspection is appropriate in the interpretation of the data.

A factor not considered by Mori and colleagues but that may have considerable relevance to the present study is myocardial stunning [1]. Recovery of myocardial function during reperfusion often requires several days for completion [2]. Bolli and associates [3, 4] have shown that even when ischemia-induced mechanical dysfunction is 100% reversible it takes at least 48 hours of reperfusion for systolic and diastolic function to recover maximally from stunning. Mechanical function was monitored only during the first 24 hours of reperfusion in the present study. This does not permit an assessment of whether the hemodynamic improvement provided by nicardipine was sustained or whether the effect of nicardipine merely reflected a hastening of recovery from stunning.

In Figure 1 I have defined a type-A intervention as one that provides additional protection to that resulting from recovery from stunning and a type-B intervention as one that merely hastens recovery from stunning. If we accept that equivalent patient survival and recovery of health both with and without nicardipine is indicative of equivalent recovery of myocardial function, then it could be argued from the data of Mori and associates that nicardipine is more likely to be a type-B intervention than a type-A.

However, in reality it is not possible to draw any definite conclusion from the present data because cardiac function was not assessed after 24 hours. If it were the case that ultimate recovery from stunning in the drug-free control patients was 100% then the present protocol could be criticized on the grounds that it offered no scope for distinguishing between type-A and type-B activity, because demonstration of type-A activity requires a recovery of function in controls of less than 100%.

Finally, if we consider the obvious improvement in laboratory variables (hemodynamic status and CK-MB release) afforded by nicardipine during the first 24 hours of reperfusion in relation to the final clinical outcome then two factors arise. First, it would appear that the laboratory variables have no prognostic significance in the present setting, and second, it would seem clear that the protocol of cardioplegia presently employed is perfectly adequate and without the need for any additives.

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Reduction of Myocardial Injury With Verapamil Before Aortic Cross-Clamping

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The effect of verapamil administered before aortic cross-clamping was assessed in 40 patients undergoing elective coronary artery bypass grafting. Myocardial protection consisted of cold blood potassium cardioplegia, topical ice slush, and moderate (28°C) systemic hypothermia. Patients were randomly divided into two groups: group 1 (18 patients) received verapamil (0.1 mg/kg up to 10 mg) intravenously three to five minutes before aortic cross-clamping; group 2 (22 patients) did not (control). Myocardial injury was assessed by cumulative release of the cardiac-specific isoenzyme of creatine kinase (CK-MB) after release of the aortic cross-clamp. Release of CK-MB was significantly lower in the verapamil group (44.9 ± 6.2 versus 72.2 ± 9.0 IU at 24.5 hours, $p = 0.005$). Calculated total infarct size was also lower in the verapamil group (6.0 ± 0.9 versus 8.9 ± 1.0 g-Eq, $p = 0.035$). Individual CK-MB release curves showed either one or two peaks. The two-peak pattern was more frequent in control patients (18 of 21 control patients versus 6 of 18 verapamil patients, $p = 0.001$) and was associated with a larger infarct size. Atrioventricular pacing was not required in any verapamil patient, but was needed in 1 control patient. We conclude that verapamil administered before aortic cross-clamping protects against myocardial injury during coronary artery bypass grafting with no increase in the incidence of atrioventricular block.

(Ann Thorac Surg 1990;49:419–23)

Hypothermic, hyperkalemic cardioplegia is the predominant technique of myocardial preservation during cardiac operations. Although this technique is good, it remains imperfect, so that some myocardial injury may occur during the period of aortic cross-clamping. Better methods of myocardial protection are constantly being sought. Data from animal experiments [1–9] have indicated that calcium-channel blockers, such as verapamil, protect myocardium from ischemic injury. These drugs were either added to the cardioplegic solution or administered before aortic cross-clamping [1–12]. Guffin and colleagues [11], in a clinical study, showed that verapamil might be useful as a pretreatment before aortic cross-clamping but was associated with increased pacing requirements when administered during the cross-clamp period. Their conclusions regarding the beneficial effects of verapamil were based primarily on hemodynamic data, which were inconclusive [11, 13].

Current methods of myocardial protection appear to be sufficiently good that significant hemodynamic differences are unlikely to be apparent under clinical circumstances. The present study was undertaken to assess the protective effect of pretreatment with verapamil using the more sensitive measurements of cumulative release of the cardiac-specific isoenzyme of creatine kinase (CK-MB) and calculated "infarct size."

Material and Methods

Patient Population

The experimental protocol was approved by the Human Subjects Review Committee, and informed consent was obtained in each case. The study group consisted of 40 adult patients with coronary artery disease undergoing elective coronary artery bypass grafting who were randomized into two groups: verapamil (group 1, n = 18) and control (group 2, n = 22). Patients in group 1 received verapamil (0.1 mg/kg up to 10 mg) in the cardiopulmonary bypass circuit three to five minutes before aortic cross-clamping. Group 2 acted as a control. Ventricular function was assessed by the ventricular wall motion score used in the Coronary Artery Surgery Study [14]. Patients receiving calcium-channel blocker or β-blocker therapy were continued on these drugs until midnight before operation.

Surgical Technique

All operations were performed by one surgeon (D.H.T.) to reduce any possible variability arising from different surgeons. All coronary arteries with a diameter greater than 1.0 mm that had 50% or greater stenosis were bypassed. All distal anastomoses were performed during a single period of cross-clamping. The proximal anastomoses were performed after removal of the cross-clamp, using a partial-occluding clamp.

Myocardial preservation consisted of cold (4°C) blood potassium cardioplegia (300 mL of Plasmalyte-A [Travenol, Deerfield, IL] plus 700 mL of blood from bypass circuit, with potassium chloride added to achieve a final concentration of 15 mEq/L). The initial dose was 400 mL, with an additional dose of 100 mL administered every 20

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minutes. The heart was packed in iced saline slush and rested on a plastic foam pad.

Cardiopulmonary Bypass Methods

Standard bypass techniques were used, with a Bentley (American Bentley, Irvine, CA) or Sarns (Sarns, Ann Arbor, MI) membrane oxygenator, a roller pump, moderate systemic hypothermia (28°C), and moderate hemodilution (hematocrit, 26%).

Anesthesia

Anesthesia techniques were standard, with intravenous fentanyl (70 to 75 μg/kg) for anesthesia, vecuronium bromide for muscle relaxation, and midazolam hydrochloride for amnesia.

Sample Collection and Analysis of Enzymes

Blood samples (3 mL) were collected 30 minutes after release of the aortic cross-clamp and every two hours thereafter, up to 12.5 hours; additional samples were collected at 18.5, 24.5, 36.5, and 48.5 hours.

The level of cardiac-specific serum CK-MB isoenzymes was measured using Roche isoimmune CK immunochemical kits (Roche, Nutley, NJ) at 37°C. Cumulative CK-MB release up to time t, $\text{CK-MB}_{r(t)}$, was calculated according to the method of Roberts and co-workers [15]:

$$\text{CK-MB}_{r(t)} = \int_0^t f(t)dt = E(t) + K_d \int_0^t E(t)dt,$$

where E(t) is the activity of CK-MB in blood in international units per milliliter, f(t) is the rate of change of CK-MB activity due to release of enzyme by the heart, and K_d is the fractional rate of disappearance of CK-MB from blood (per minute).

Infarct size at time t, IS(t), was calculated from serial CK-MB plots as described by Rao and colleagues [16] according to the formula of Roberts and co-workers [15]:

$$IS(t)_{\text{CK-MB,g-Eq}} = \frac{\text{CK-MB}_{r(t)} \cdot K_d \cdot DV \cdot \text{body weight(g)}}{\text{pCK-MB} \cdot (\text{CK-MB}_{\text{normal}} - \text{CK-MB}_{\text{infarcted}})},$$

where $\text{CK-MB}_{r(t)}$ = the area under the CK-MB time curve; K_d = 0.0017 (decay constant determined in 10 patients with uncomplicated myocardial infarction); distribution volume (DV) = 44 mL/kg; and pCK-MB (proportion of CK-MB released into blood as compared with CK-MB depleted from heart) = 0.15; temperature correction for normal and infarct-depleted values: $\text{CK-MB}_{\text{normal}}$ = 280 U/g wet tissue and $\text{CK-MB}_{\text{infarcted}}$ = 77 U/g wet tissue at 37°C, instead of $\text{CK-MB}_{\text{normal}}$ = 136 U/g wet tissue and $\text{CK-MB}_{\text{infarcted}}$ = 35 U/g wet tissue at 30°C [16].

Statistical Analysis

Statistical anaylsis was made by unpaired *t* test for continuous variables or Fisher's exact test for discrete variables. Analysis of differences in CK-MB release was performed by Bruce Levin, PhD, of the Division of Biostatistics, Columbia University School of Public Health, in the following manner. For each group, the mean intercept and mean slope parameters were estimated by maximum likelihood using weighted averages to account for varying patterns of observtions per patient. Hotelling's T^2 statistic for the bivariate vector parameter of intercept and slope was used to determine statistical significance.

Table 1. Patient Population[a,b]

Variable	Verapamil (n = 18)	Control (n = 22)
Age (yr)	67.6 ± 7.7	63.2 ± 10.1
Age range (yr)	53–84	47–79
M:F	16:2	18:4
Preoperative Ca^{2+} blockers[c] (%)	66.7	72.7
95% CL	41.3–85.5	49.7–88.3
Ventricular score[d]	13.3 ± 3.4	13.6 ± 3.6
Grafts	2.9 ± 0.8	2.9 ± 0.8
CPB time (min)	107 ± 20.8	114 ± 22.8
Cross-clamp (min)	56 ± 16.1	61 ± 16.5

[a] Where appropriate, values are given as mean ± standard deviation. [b] p = not significant for all variables. [c] Diltiazem, nifedipine, or verapamil. [d] Determined as described in [14].

CL = confidence limits; CPB = cardiopulmonary bypass.

Results

The ages, sex, number of grafts, preoperative calcium-channel blockers, ventricular scores, cardiopulmonary bypass times, and cross-clamp times did not differ significantly (Table 1). One patient in the control group had a perioperative myocardial infarction by electrocardiographic criteria (new Q waves) but otherwise recovered without incident. This patient was excluded from analysis because we believed that enzyme elevations due to perioperative myocardial infarction might bias the results unfairly. There were no deaths and no other clinically significant complications.

There was no significant difference in the need for postoperative inotropic support (dopamine or dobutamine) in the verapamil group (3 of 18 = 0.167; 95% confidence limits [CL], 0.045 to 0.421) versus the control group (4 of 21 = 0.190; 95% CL, 0.064 to 0.424).

Cumulative CK-MB release was significantly lower in the verapamil group (p = 0.005). This difference was present in the initial sample at 30 minutes (5.2 ± 0.7 versus 7.0 ± 1.3 IU, mean ± standard error of the mean) and increased to 30.2 ± 2.9 versus 40.5 ± 5.1 IU at 12.5 hours, to 47.4 ± 6.1 versus 61.6 ± 11.4 IU at 24.5 hours, and to 56.4 ± 8.6 versus 61.6 ± 11.4 at 36.5 hours (Fig 1).

The infarct size was calculated at the time of the first peak in the CK-MB activity curve (infarct size-1; 4.5 to 6.5 hours) and for the entire curve (infarct size-total; 48.5 hours). Infarct size-1 did not differ significantly between the two groups (verapamil, 3.2 ± 0.3 g-Eq [standard error of the mean], versus control, 3.1 ± 0.07; p = 0.74). However, infarct size-total was significantly lower in the verapamil group (6.0 ± 0.9 versus 8.9 ± 0.97 g-Eq; p = 0.035) (Fig 2).

There were two distinct patterns of CK-MB activity: one peak versus two peaks. The first peak occurred at 4.5 to 6.5 hours. The "two-peak" pattern showed a second peak of activity at 18.5 to 24.5 hours (Fig 3) and was associated

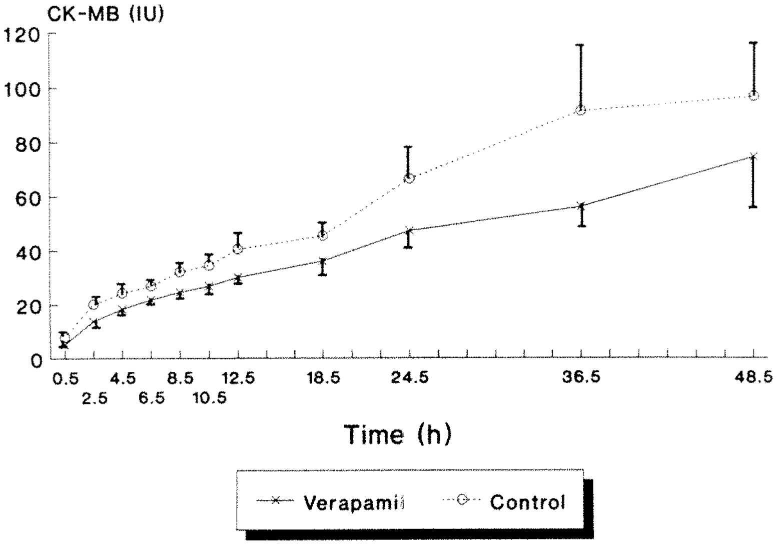


Fig 1. Cumulative CK-MB release curves showing that CK-MB release is lower in the verapamil group. The difference is highly significant (p = 0.005). Time is measured from release of the aortic cross-clamp. Error bars represent one standard error of the mean.

with a larger infarct size, implying more myocardial injury in such patients. Only 6 of 18 verapamil patients had this two-peak pattern (0.33; 95% CL, 0.145 to 0.587), but 18 of 21 control patients had such a pattern (0.86; 95% CL, 0.628 to 0.962; $p = 0.001$).

It is our standard practice to use atrial pacing if the spontaneous sinus rate is less than 80 beats per min. When this standard was applied the verapamil group had a much greater need for temporary atrial pacing (16 of 18) than did the control group (9 of 21) (Fig 4); however, none of the patients in the verapamil group had atrioventricular block. In 1 patient in the verapamil group, atrial fibrillation developed after weaning from cardiopulmonary bypass; this patient required ventricular pacing. One patient in the control group required temporary atrioventricular pacing for atrioventricular heart block.

Comment

Use of calcium-channel blockers to protect myocardium during periods of ischemia was based on the hypothesis that excessive calcium entry into cells during postischemic reperfusion may activate the actinomycin adenosine triphosphatase enzyme system, causing excessive hydrolysis and depletion of adenosine triphosphate [1]. Furthermore, excessive concentrations of intracellular phosphate and calcium may also cause ultrastructural damage by precipitating to form insoluble complexes within the mitochondria [1, 4]. Calcium-channel blockers were thought to have the potential to block such pathological occurrences.

Using animal models, earlier workers added calcium-channel blockers, including nifedipine, diltiazem, and verapamil, to the cardioplegic solution as either a supplement or a substitute for potassium [1–9]. The data from these studies indicated several beneficial effects, including preservation of mitochondrial ultrastructure, improved hemodynamic recovery, and reduced enzyme leakage. Encouraged by these results, Clark and co-workers [12] undertook a clinical trial of nifedipine in cardioplegia and found improved hemodynamics and reduced CK-MB

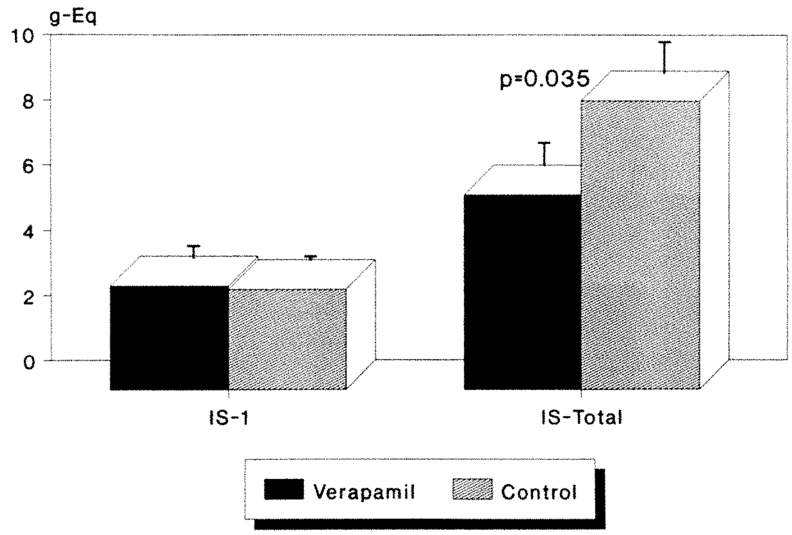
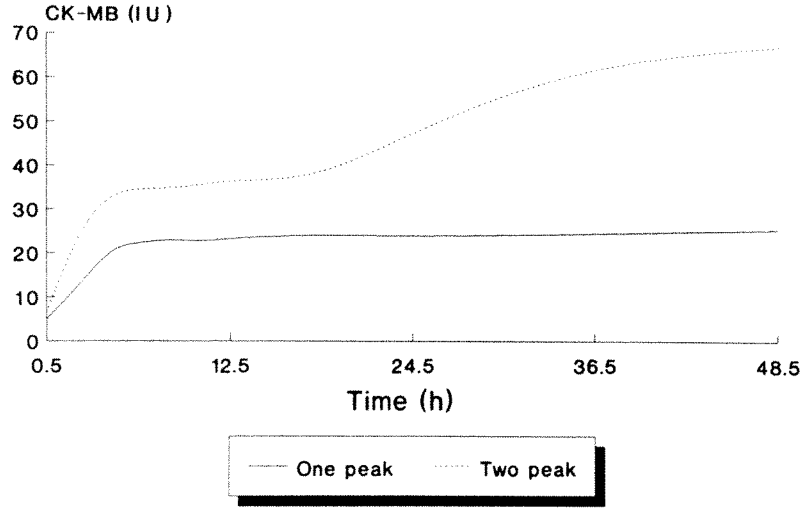


Fig 2. Calculated infarct size (IS). Infarct size at 4.5 to 6.5 hours (IS-1) is not significantly different between the two groups. Infarct size (IS-Total) at 48.5 hours was significantly lower in the verapamil group (p = 0.035).

Fig 3. Representative curves showing the one-peak and two-peak patterns of cumulative CK-MB release. The two-peak pattern was associated with a larger infarct size and was significantly more common in the control group (p = *0.001).*



isoenzyme release. However, widespread intraoperative use of these drugs has been hampered by the fact that all the major calcium-channel blocking agents may reduce blood pressure [13] and, when added to the cardioplegic solution, increase the incidence of temporary atrioventricular block [11, 17]. Guffin and colleagues [11] divided their patients into four groups: intravenous verapamil before cross-clamping, intravenous verapamil plus verapamil in the cardioplegic solution, verapamil in the cardioplegic solution only, and a control group. There were only 7 to 9 patients in each group. The two groups receiving verapamil in the cardioplegic solution required atrioventricular sequential pacing in 25% and 33% of cases, respectively, as compared with 14% of those receiving verapamil before aortic cross-clamping [11].

Baraka and colleagues [10] pretreated 12 of 22 patients with verapamil (0.075 mg/kg) before aortic cross-clamping. The hemodynamic variables after cardiopulmonary bypass were comparable in the two study groups. The occurrence of heart block and the need for ventricular pacing were frequent in both groups (6 of 10 control and 10 of 12 verapamil patients) but were not significantly different. The verapamil group was more readily defibrillated and had fewer ischemic electrocardiographic changes, which were considered indications that verapamil pretreatment may potentiate the myocardial protective effects of cardioplegia.

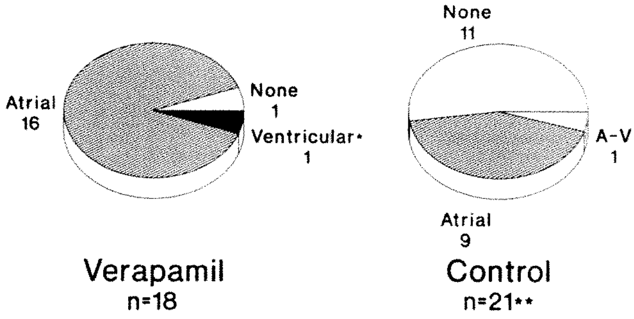


Fig 4. Temporary pacing requirements. All patients with heart rate less than 80 beats per minute had atrial pacing. (A-V = *atrioventricular sequential pacing; *One patient had atrial fibrillation postoperatively; **One patient was excluded due to perioperative myocardial infarction.)*

In the present study, none of the patients receiving verapamil before aortic cross-clamping experienced atrioventricular block, as compared with 1 patient in the control group. The dose of verapamil (0.1 mg/kg) was chosen because it lay at the approximate midpoint of the recommended dosage range (0.075 to 0.150 mg/kg) [18]. Sixteen of 18 patients in the verapamil group required temporary atrial pacing to maintain a rate of at least 80 beats per minute, as opposed to only 9 of 21 control patients. This decrease in the sinus rate may actually be a desirable effect of verapamil, as uncontrolled sinus tachycardia may increase myocardial oxygen consumption.

The study by Guffin and colleagues [11] relied primarily on hemodynamic measurements to demonstrate improvement and was inconclusive [13]. The need for more sensitive indicators of myocardial injury was apparent. Roberts and co-workers [15] used CK-MB isoenzyme kinetics to quantify myocardial infarction as early as 1975. Their methods have been of particular interest to cardiac surgeons, due to the difficulties in diagnosing perioperative myocardial infarction after coronary artery bypass grafting [16, 19, 20].

The term *CK-MB release* refers to the cumulative amount of CK-MB released into the blood by the heart, rather than a simple determination of CK-MB activity. The calculation involves the fractional disappearance of the CK-MB isoenzyme, as well as the integral under the curve of CK-MB activity versus time [15].

There were two different patterns of CK-MB release curves (see Fig 3): the single-peak curve, which was present in 67% of the verapamil group and was associated with a smaller CK-MB release, and the double-peak curve, which was present in 86% of the control group and was associated with a larger CK-MB release. We believe that the appearance of the first peak results from surgical manipulation of the heart. The second peak appears to represent a secondary release of CK-MB, indicating additional myocardial injury. Quantification of isoenzyme release appears to be a more sensitive index of myocardial preservation than hemodynamic data, as hemodynamic performance is dependent on many factors other than myocardial injury, including anesthesia, drug therapy, and loading conditions.

The results of this study show a decrease in both CK-MB release and infarct size in the verapamil group. There was no increase in atrioventricular block. Verapamil administered before aortic cross-clamping appears to be a safe and effective adjunct to current methods of myocardial preservation.

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Potential Role of Dendritic Cells in Bronchiolitis Obliterans in Heart-Lung Transplantation

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Dendritic cells are essential for the activation of the type IV immunological reactions that are intrinsic to rejection of transplanted organs. We evaluated the number of dendritic cells in the recipient and donor portions of the trachea and donor bronchi of 6 heart-lung transplant recipients, 3 of whom had evidence of bronchiolitis obliterans, a presumed manifestation of chronic rejection of the lung. As compared with recipients without bronchiolitis obliterans, patients with it showed a significant increase in the number of S100-protein–positive dendritic cells in the tracheal and bronchial epithelium and submucosa of the donor organs. This finding of increased accessory cells in the transplanted mucosa provides support for the belief that bronchiolitis obliterans is an immunologically mediated form of chronic rejection.

(*Ann Thorac Surg 1990;49:424–8*)

In the early 1980s it was recognized that activation of type IV immunological reactions by lymphocytes required the participation of cells of the mononuclear phagocyte system [1–4]. These antigen-presenting cells, particularly dendritic cells (DCs), were responsible for processing raw antigens and then presenting appropriate epitopes to the lymphoid population [5, 6]. Once primed, these lymphocytes underwent blastogenesis and clonally restricted expansion, and induced the effector arm of the immune response. Nowhere does this process need to exist to a greater extent than in the lung, where antigenic material is presented by aerogenous, lymphatic, and hematogenous routes. Yet only recently have investigators [7–14] reported on the presence of a normal dendritic cell population in the lung that is particularly activated during cigarette smoking and Langerhans cell granulomatosis.

Since 1980 heart-lung and unilateral lung transplantation have become viable therapeutic options in individuals with end-stage pulmonary disease. Once through the initial postoperative period, over 50% of patients experience an unrelenting process of airway injury corresponding histologically to bronchiectasis and bronchiolitis obliterans (OB) [15, 16]. Evidence from many areas suggests that OB represents a consequence of immunological injury to the respiratory epithelium, and it seems logical that dendritic cells may play a role in the local microenvironmental alterations that predispose to the large and small airway rejection [17, 18]. To this end, we undertook a study to investigate whether alterations in the number of dendritic cells occurred within the trachea and bronchi of heart-lung transplant (HLT) recipients with and without OB.

Material and Methods

Four groups of 3 patients each who underwent autopsy examination constituted the study groups: (A) 3 patients who had died of nonthoracic causes and at autopsy examination lacked evidence of inflammatory lung disease; (B) 3 patients who had undergone organ transplantation other than the heart and lungs, were being treated with cyclosporine and steroids, and died of nonthoracic causes; (C) 3 patients who had undergone heart-lung transplantation but died of causes other than OB and had no evidence of OB before or at autopsy examination; (D) 3 HLT recipients who had premortem biopsy specimens demonstrating OB and died of the consequences of terminal obstructive airways disease. Survival of the HLT recipients ranged from 108 to 1,106 days. There was no significant difference between the groups relative to length of steroid and cyclosporine therapy, pulmonary infection at the time of death, history of cytomegalovirus or *Pneumocystis* infection before death, HLA mismatch of donor and recipient, cause of clinical pulmonary hypertension, or sex, age, or race of recipient or donor.

Similar histological sections were taken from all groups. In groups A and B, sections were taken of the trachea three rings above the carina and the left upper lobe bronchus 1 cm beyond its bifurcation with the left lower lobe. In HLT recipients, sections were taken above the tracheal anastomotic line (recipient trachea), below the anastomosis (donor trachea), and from the left upper lobe bronchus (donor bronchus). Trachea or bronchus, or both, was fixed in neutral buffered formalin, embedded in paraffin, sectioned at 4 μm, and routinely stained with hematoxylin and eosin. Four-micrometer sections were stained with polyclonal rabbit antibody to S100 protein [19] (Dako Patts Co, Inc, Santa Barbara, CA; dilution, 1:1000; incubation, 18 hours at 4°C in moisture chambers) for the detection of DCs using the avidin-biotin complex

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Table 1. Number of Dendritic Cells/10 mm^2 Within Epithelium and Submucosa of Trachea and Left Upper Lobe Bronchus

	Trachea Recipient			Trachea Donor			Bronchus Donor		
Group	E	S	Total[a]	E	S	Total[a]	E	S	Total[a]
Normal									
1	84	21	105	N/A	N/A	N/A	34	23	57
2	18	57	75	N/A	N/A	N/A	0	72	72
3	0	12	12	N/A	N/A	N/A	0	49	49
Mean	34	30	64				11	48	59
Transplant control									
1	33	191	224	N/A	N/A	N/A	194	17	211
2	64	27	91	N/A	N/A	N/A	58	18	76
3	20	53	73	N/A	N/A	N/A	33	24	57
Mean	39	90	129				95	20	115
HLT without OB									
1	33	67	100	60	21	81	0	13	13
2	27	6	33	27	25	52	35	27	62
3	0	26	26	7	22	29	4	27	31
Mean	20	33	53	31	23	54	13	22	35
HLT with OB									
1	62	106	168	30	14	44	42	61	103
2	24	73	97	48	67	115	11	112	123
3	191	25	216	78	218	296	71	202	273
Mean	92	68	160	52	100	152	41	125	166

[a] Total number of dendritic cells in epithelium and submucosa.

E = epithelium; HLT = heart lung transplant; N/A = not applicable; OB = bronchiolitis obliterans; S = submucosa.

method of Hsu and co-workers [20]. Secondary antibody incubation (goat antirabbit; Dako Patts Co, Inc; dilution, 1:300; incubation, 1.0 hour at 4°C in moisture chamber) was followed by chromogenic visualization by immersion in 3,3-diaminobenzidine solution (0.25 mg/mL) with 0.003% hydrogen peroxide for a maximum of ten minutes. The sections were subsequently dipped in 0.125% osmium tetroxide solution, rinsed in tap water, counterstained with Harris' hematoxylin, dehydrated in graded alcohols and Americlear, and coverslipped with a synthetic mounting medium. Nerve twigs of the bronchial submucosa and chondrocytes acted as positive internal controls.

For the purpose of this study, a dendritic cell was defined as an S100-protein–positive cell with a roughly oval but irregularly shaped nucleus with a central cleft and cytoplasm that formed dendritelike processes between adjacent cells [21]. Cells in which the nucleus could not be discerned or in which the cytoplasm lacked dendritic processes, but that were S100-protein–positive, were not included as true dendritic cells.

Cells were counted using an ocular micrometer with an ocular grid. The grid (ocular test system; Carl Zeiss, Oberhochen, FRG) was inserted into the eye piece of the microscope and the divisions of this grid (1 square = 0.000625 mm^2) were used to measure the area of bronchiolar epithelium and underlying submucosa. In all samples an area of bronchial epithelium corresponding to at least 5 mm^2 and a submucosal area of 15 mm^2 were evaluated. Dendritic cells were counted within the epithelium above the basement membrane (average height, 0.0375 mm) and 0.125 mm below the basement membrane. Adipocytes and Schwann cells from submucosal nerve twigs were carefully excluded.

Results

The results of this preliminary study are presented in Table 1, where the number of DCs are expressed as the number per 10 mm^2. The normal and transplant controls showed marked variation in the number of cells within the tracheal epithelium (range, 0 to 84) and within the submucosa (range, 12 to 191). The variation was also noted in the bronchial epithelium (range, 0 to 194) and submucosa (range, 18 to 72).

Perhaps the most notable trend was present in the heart-lung recipient group with OB. In general, whether in donor or recipient epithelium, the number of DCs was increased relative to that of the control groups and HLT recipients without OB. This finding held true for both the intraepithelial and submucosal DCs; the tracheal epithelium and submucosa displayed an average sum total of 160 (recipient) and 152 (donor) in the patients with OB in contrast to 53 and 54 in the HLT recipients without OB. The number of DCs in the left upper lobe bronchus of patients with OB was similarly increased (166 versus 35). This overall increase was also noted when compared with the two controls.

It is also evident that the increase in DCs in the OB group also included the recipient trachea, in addition to

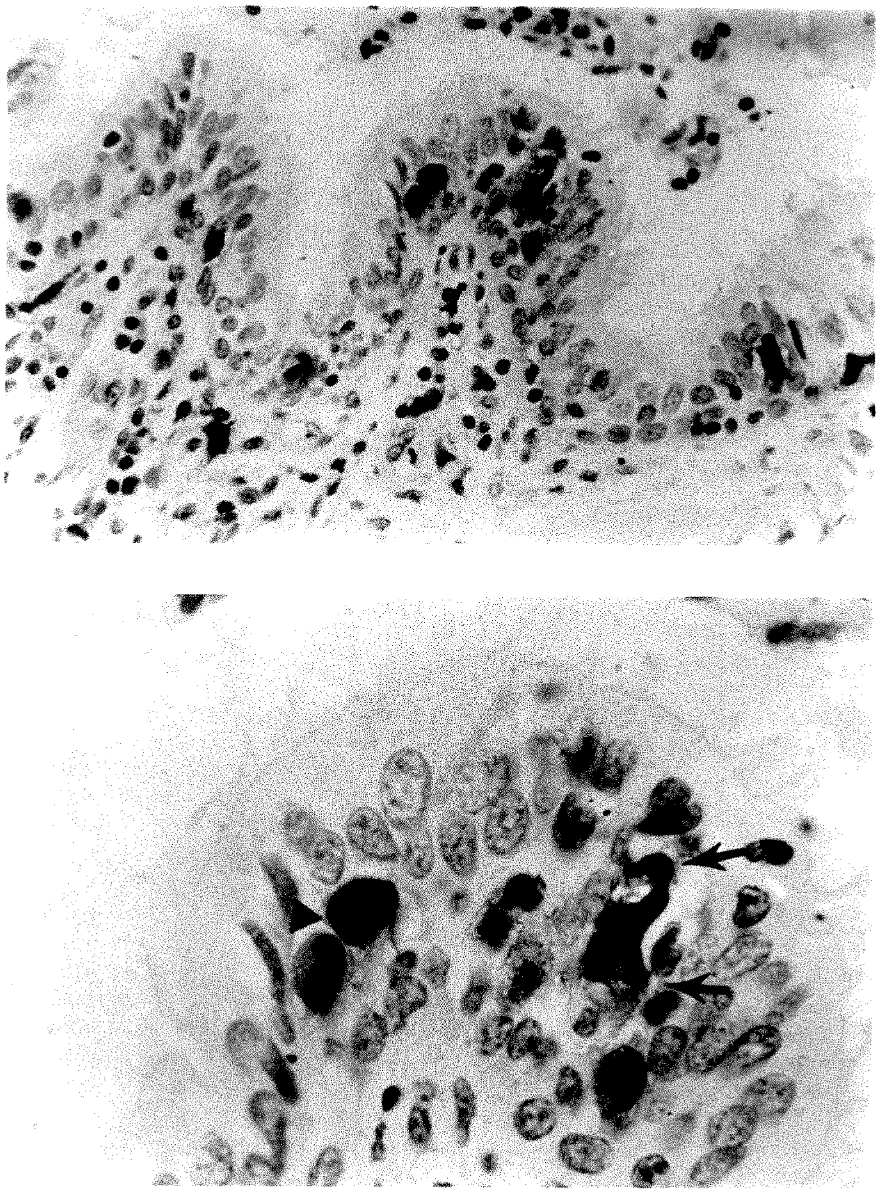

Fig 1. (A) S100 protein immunostains decorated the folded reniform nuclei of the intraepithelial and submucosal dendritic cells. (B) Within the epithelium, the stellate arborizing cell processes (arrows) *of the dendritic cells were accentuated by this immunostain. (Immunoperoxidase; A, ×315; B, ×500).*

the donor sites. Similarly, comparing OB patients with patients having organ transplants other than heart-lung reveals that both groups have increased numbers of DCs relative to normal patients and HLT recipients without OB.

The dendritic cells within the epithelium resided in the lower half of the pseudostratified epithelium (Fig 1). The nuclei were reniform or oval with prominent nuclear clefts and folds. Cytoplasmic processes were stellate and insinuated between epithelial cells. They were occasionally associated with clusters of lymphocytes and were distributed in small aggregates within both the epithelium and submucosa.

Comment

Dendritic cells are bone-marrow–derived cells having a life span of three to five days and can be found in many disorders involving defects in immunomodulation including ulcerative colitis and rheumatoid arthritis [1, 4]. Pulmonary DCs are found primarily in the bronchial and bronchiolar epithelium, their submucosa, and the alveolar mesenchyme, and they have a role analogous to that proposed for DCs in the skin in activating the afferent limb of the immune response [21–23]. They are known to increase in number in response to cigarette smoking [7], fibrosing processes of lung especially usual and desquamative interstitial pneumonia [8], and eosinophilic granuloma of lung [24], and within the stroma of infiltrating primary adenocarcinomas of lung [14]. They may migrate to regional lymph nodes, especially the paracortex, where they aid in eliciting T-cell–mediated reactions [25]. It seems reasonable to suspect that local microenvironmental and cellular, eg, dendritic cell, alterations in the airways of HLT recipients may play a role in chronic rejection of the graft, which morphologically corresponds to OB.

The data presented herein suggest that these HLA class II antigen–positive DCs within the graft may be a source for presenting antigens responsible for graft rejection alloreactive lymphocytes. It has been recognized in some animal models that selective depletion of donor DCs by pretreatment with antidendritic cell antibody can lead to prolongation of graft survival [26, 27]. In studies by Raftery and associates [28], it has also been noted that DCs are increased in numbers during episodes of renal allograft rejection. Our study suggests that the presumed immunologically mediated bronchitis/bronchiolitis of chronic rejection of the lung is associated with increased numbers of recipient DCs within the target epithelium. The DCs presumably activate local and systemic rejection responses because they are active stimulators of lymphocyte responses in culture, and may augment the primary mixed lymphocyte response over 100 times when added to fractionated spleen cell suspensions [29].

Our findings indicate that DCs are increased in the tracheal and bronchial epithelium and submucosa of patients with OB in particular. However, the increase was also seen in non-HLT organ recipients and the recipient tracheas of the recipients with OB. This may reflect some nonspecific stimulation of DC migration into the lungs, especially as both groups are predisposed to infection by virtue of their immunocompromised states. However, there does seem to be a trend within the HLT groups that patients with OB had substantially greater numbers of DCs than those of their nonrejecting counterparts. This trend provides support for the role of DCs in OB in this transplant cohort despite the variability in numbers and small study size.

Toews and colleagues [12, 29] have also shown that contact sensitivity responses in the skin of DC-enriched epidermis shows a marked increase in the proliferation of T cells and macrophages. It is their belief, as well as that of others, that bone-marrow–derived DCs migrate to the epithelial structures, including bronchial epithelium, and, because of their shared class II antigens, interact with unprimed or quiescent T cells to trigger a local effector inflammatory cascade. This reaction in turn generates an alloreactive immune response directed at donor-derived bronchial epithelium, eg, OB, which is mediated by α- and γ-interferon. These cytokines may enhance class II antigen expression on bronchial epithelium by increasing or stimulating expression of new surface alloantigens, further enhancing the rejection process. Such studies suggest that inhaled stimuli, especially pneumonias due to cytomegalovirus and *Pneumocystis*, may increase the number and activity of DCs within the epithelium with nonspecific upregulation of the rejection episode. This finding has been supported in clinical studies by Paradis and co-workers [16]. Migration of DCs to recipient bronchial-associated lymphoid tissue, spleen, or lymph nodes may also activate a systemic response.

Several deficiencies exist in a preliminary study of this kind. First, recognizing the short life span of DCs of three to five days, it is assumed that the cells counted are in fact recipient derived. Unfortunately frozen tissue and HLA typing were unavailable in these patients, so double-labeling immunoperoxidase evaluations could not be performed. It should also be recognized that S100 protein does not identify all DCs involved in accessory cell processing functions. Many other cells may be involved, including alveolar macrophages [21]. Second, the recipients of HLT are immunodeficient and are exposed to many polymicrobial infections and exogenous antigenic stimuli during the course of their illness, which may account for the increased number of DCs. This argument has support in that the OB group and control transplant group both showed the greatest increase in numbers of DCs. Third, these are static studies and may not truly reflect the proposed immunological mechanisms. Finally, variations in the number of DCs in the control and study groups are possible given the limited sites of tissue study.

Future studies of the role of DCs and rejection may be worthwhile. They include selective depletion of the graft or recipient hematolymphoid tissue of DCs, examination of the role of DCs in the lymphocytic bronchiolitis seen in bone marrow transplant recipients, the study of DC populations in bronchoalveolar lavage fluid, and more extensive phenotypic characterizations of the endogenous accessory cell network in lung allografts.

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Transatrial Relief of Diffuse Subaortic Stenosis After Ventricular Septal Defect Closure

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Transatrial enlargement of the left ventricular outflow tract for serious obstruction was performed in 3 patients with previous ventricular septal defect closure. Two patients had recurrent subaortic stenosis as resection had already been performed at initial operation. In all patients, the obstruction was located below the ventricular septal defect patch. Patch enlargement of the left ventricular outflow tract was carried out by opening the ventricular septal defect patch through the tricuspid valve and extending the incision downward through the area of obstruction and the left ventricular body. All patients had uneventful postoperative course and effective relief of left ventricular outflow tract obstruction. We feel that the approach is simple and effective; it avoids a right ventriculotomy and provides a viable option in certain patients with left ventricular outflow tract obstruction.

(Ann Thorac Surg 1990;49:429–34)

Effective relief of diffuse obstruction of the left ventricular outflow tract requires an aggressive surgical approach. Aortoventriculoplasty [1–4], left ventricular apicoaortic conduit insertion [5–7], and modified Konno procedure have been used. The modified Konno procedure [8, 9] consists of opening of the infundibulum of the right ventricle, patch enlargement of the conal septum, and closure of the infundibular incision with or without a patch. Although only a limited number of modified Konno procedures have been reported, it is preferable because the native aortic valve is preserved. The use of a prosthetic valve as in aortoventriculoplasty or in ventriculoaortic conduit insertion is avoided.

In the last 3 years, we have successfully performed eight left ventricular outflow tract enlarging procedures. In three of these, a subaortic ventricular septal defect has

Table 1. Clinical Summary

	Cardiac Catheterization (C) or Echocardiography (E)			Pressure							
Patient No.	No.	Age (yr)	Qp/Qs	RV (mm Hg)	LV (mm Hg)	OG (mm Hg)	LVOT Gradient (mm Hg)	Initial Operation (age)	Final Operation (age)	Postop LVOT Echo Gradient (age)	Outcome
1	C1	6 mo	2.3:1	44/8	90/10	NA		VSD patch closure; SAS resection (16 mo)	LVOT patch (7 yr)	None (2 mo)	Well at 1 yr
	C2, E	5 yr					20–40				
	E	7 yr					64–70				
2	C1	3 yr	1.7:1	46/13	110/20	40		VSD closure[a]; SAS resection (3 yr)	LVOT patch; RV stenosis resection (9 yr)	None (7 mo)	Well at 1 yr
	C2	5 yr		40/80	105/12	10					
	C3	9 yr		70/12	140/20	20					
3	C1	1.5 mo	4.9:1	55/10	NA	NA		VSD patch closure (6 mo)	LVOT patch (5 yr)	None (2 mo)	Well at 6 mo
	C2	1.5 yr		29/9	107/15	30					
	C3	5 yr		. . .	130/6	50					

[a] Edges of ventricular septal defect closed (probably septal leaflet of the tricuspid valve partially closing the defect).

LV = left ventricular; LVOT = left ventricular outflow tract; NA = not available; OG = outflow gradient of the left ventricle; Qp/Qs = pulmonary to systemic blood flow ratio; RV = right ventricular; SAS = subaortic stenosis; VSD = ventricular septal defect.

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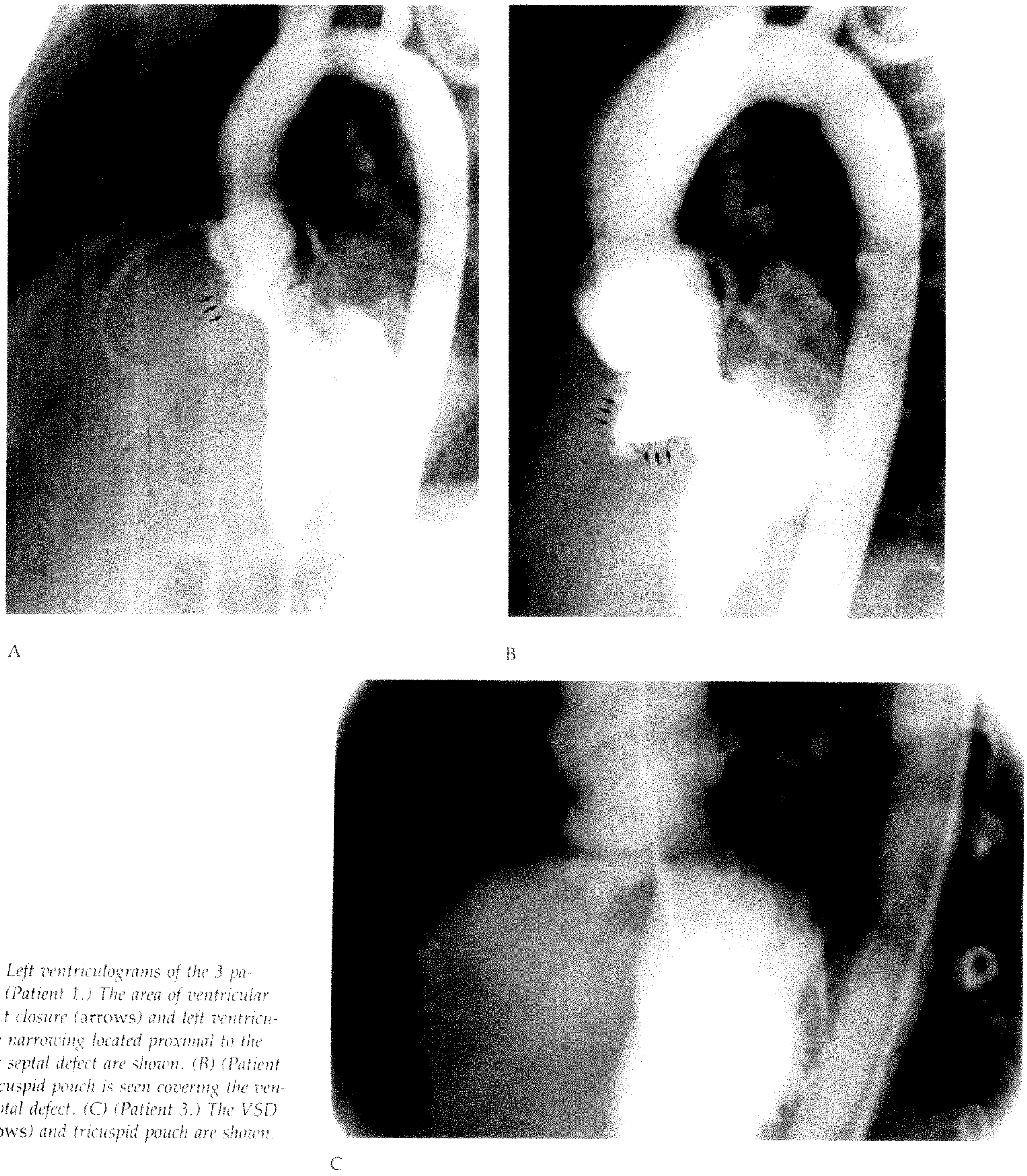

Fig 1. (A) Left ventriculograms of the 3 patients. (A) (Patient 1.) The area of ventricular septal defect closure (arrows) *and left ventricular outflow narrowing located proximal to the ventricular septal defect are shown. (B) (Patient 2.) The tricuspid pouch is seen covering the ventricular septal defect. (C) (Patient 3.) The VSD patch* (arrows) *and tricuspid pouch are shown.*

been previously closed followed by progressive left ventricular outflow tract narrowing. Instead of using the transventricular approach of the modified Konno procedure, we used a conal enlarging incision via a transatrial approach. These cases form the basis of this report.

Material and Methods

Patients

Three patients were referred to our service because of pronounced left ventricular outflow tract obstruction. The clinical summary is in Table 1. All patients had previous perimembranous septal defect closure. Two patients also had resection of discrete fibromuscular tissue obstructing the subaortic area at the time of ventricular septal defect closure. In 1 patient, resection was done because of angiographic and echocardiographic diagnosis of subaortic stenosis, although a left ventricle-to-aorta pullback could not be done. In another patient, the ventricular septal defect was closed by approximation of the edges, probably part of the septal leaflet of the tricuspid valve, which was partially closing the defect.

In all patients, left ventriculography showed the outflow tract obstruction located proximal to the ventricular

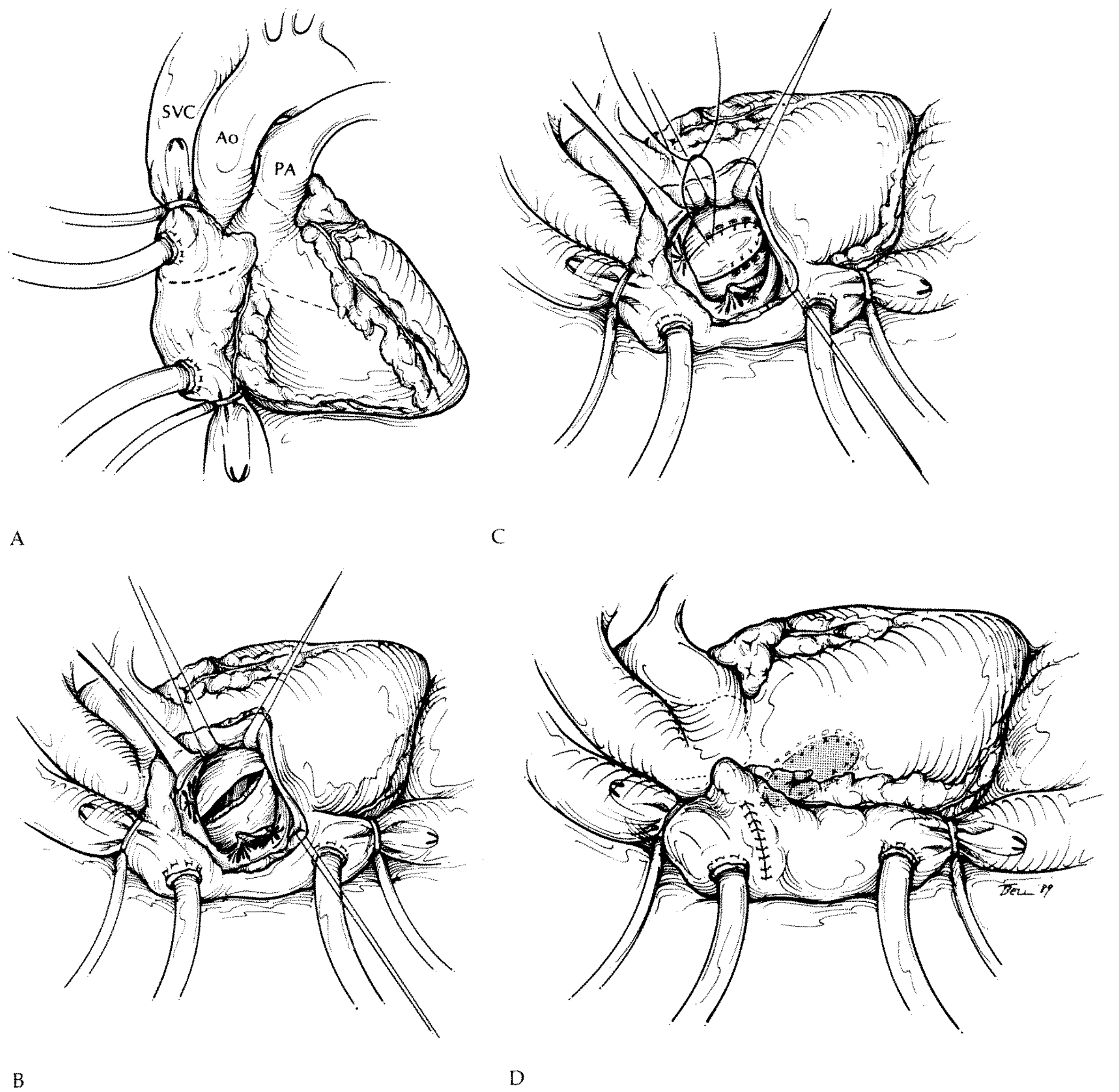

Fig 2. Surgical technique (see text for description). (A) Incisions on the right atrium and conal septum. (B) Ventricular septal defect patch, and conal septum opened down to the left ventricular body. (C) New patch is being placed. (D) Left ventricular outflow enlarging patch in place and right atriotomy closed. (Ao = *aorta;* PA = *pulmonary artery;* SVC = *superior vena cava.)*

septal defect closure (Fig 1). Left ventricular outflow tract systolic gradients were 20, 50, and 70 mm Hg. The patient with the 20-mm Hg outflow gradient who had resection at the time of ventricular septal defect closure also had a progressing right ventricular infundibular stenosis. In this patient, we decided to relieve both the right and left ventricular outflow obstructions because of high left ventricular diastolic pressure (20 mm Hg).

Because of the angiographic appearance of the left ventricular outflow tract, recurrent nature of the obstruction in 2 patients, and hypoplasia of the outflow tract on intraoperative exploration, we felt that the obstruction could be best relieved in all patients by patch enlargement of the outflow tract.

Surgical Technique

A midsternotomy incision was made. Cardiopulmonary bypass was instituted through an arterial cannula in the distal ascending aorta and two vena cava cannulas inserted far apart through the right atrial wall. A left ventricular apical sump and moderate hypothermia (25° to 28°C) were used. The ascending aorta was cross-clamped and blood cardioplegia was given through the aortic root. Ice slush was also applied topically to the heart. Through an aortotomy, the aortic valve and subaortic area were assessed for the severity and length of the stenosis to determine feasibility of simple resection. Recurrent subaortic stenosis suggested a more severe form of obstruction, which was probably best treated with enlargement of the conal septum. A transverse right atriotomy was performed; an incision was made on the ventricular septal defect patch and extended downward through the area of obstruction and left ventricular body (Figs 2, 3). The incision could be extended upward to the tricuspid or aortic annulus. Remaining obstructive fibromuscular tis-

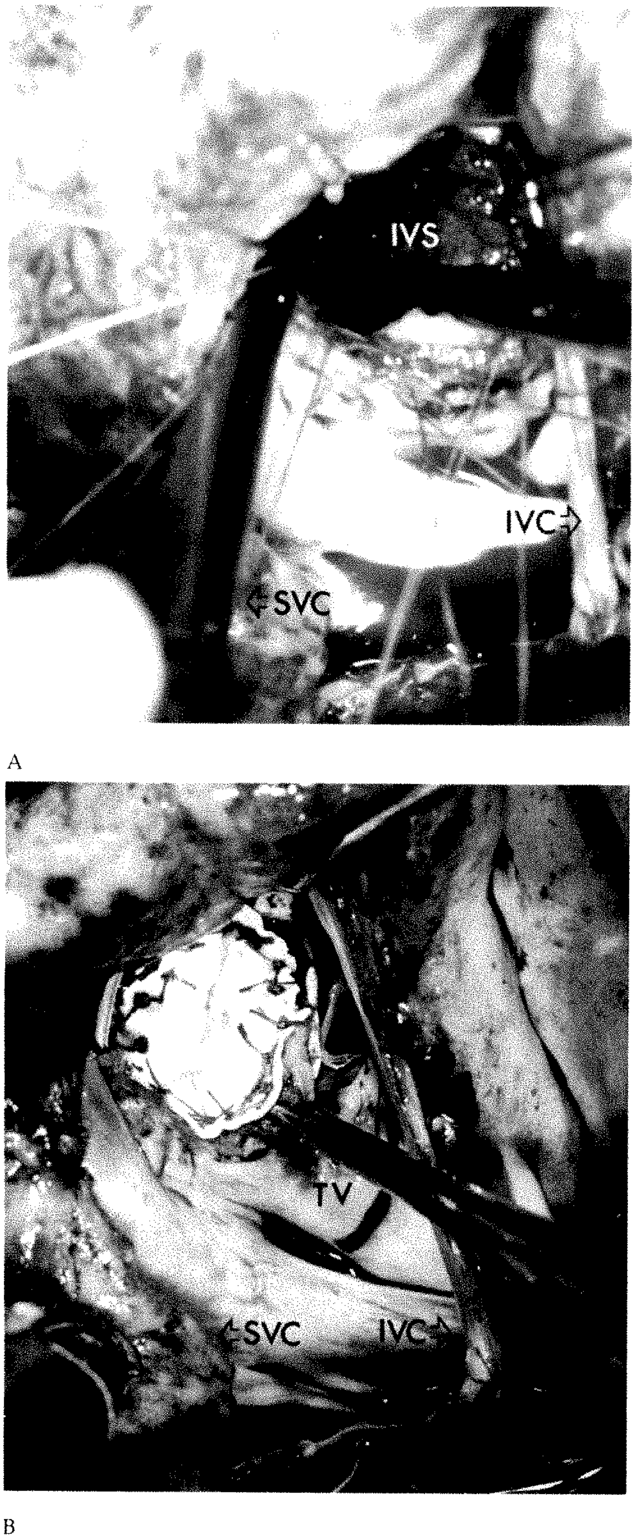

Fig 3. (A) Intraoperative photograph of patient 1 showing the conal or interventricular septum (IVS) opened through a transverse right atriotomy and tricuspid valve. (B) The patch is in place. Muscle of Lancisi is seen with the tricuspid valve (TV) attachment. (IVC = inferior vena cava; SVC = superior vena cava.)

sues could be excised through the same incision. The aortotomy was helpful in protecting the aortic valve and in ensuring relief of the outflow tract obstruction. The aortotomy was closed, and additional blood cardioplegia was given at 15- to 20-minute intervals. The left ventricular outflow tract enlarging incision was then closed with a polytetrafluoroethylene patch using interrupted pledgeted sutures. The atriotomy incision was closed and the aortic cross-clamp removed. Rewarming, weaning from cardiopulmonary bypass, and sternotomy closure were done in the usual manner.

Results

Except for a transient heart block in 1 patient, the postoperative course was uneventful. Echocardiography done at 2 to 7 months postoperatively showed no residual gradient across the left ventricular outflow tract (Fig 4). The patients are doing well 6 months to 1 year postoperatively.

Comment

Simple resection of fibromuscular tissue causing diffuse left ventricular outflow tract obstruction carries high early and late mortality rates [10, 11] because of ineffective relief of the obstruction. A more aggressive approach such as aortoventriculoplasty (Konno-Rastan [1–4]), apicoaortic conduit insertion [5–7], and modified Konno procedure [8, 9] is often necessary. However, the decision to simply resect the obstructing tissue or to use a more radical procedure can be difficult to make in borderline cases in which evaluation by angiography, echocardiography, and even operative inspection of the left ventricular outflow tract may not be easy. In these cases, simple resection followed later by a more radical procedure in the event of recurrence may be more appropriate.

Although the modified Konno procedure has been reported in only a few cases [8, 9], it is preferable in the presence of a functional aortic valve without narrow aortic annulus. Aortoventriculoplasty and apicoaortic conduit insertion involve use of a prosthetic valve. Long-standing anticoagulation and possible replacement of valve prosthesis are avoided with the modified Konno procedure.

Vouhe and colleagues [12] reported a more radical approach for resecting diffuse obstruction of the outflow tract in 2 patients. A longitudinal anterior aortotomy was performed, carried down through the annulus of the aortic valve at the commissure of the right and left cusps, and extended to the conal septum with a right infundibulotomy. After resection of the obstructing fibromuscular tissue, all incisions were closed primarily. This approach may be better than simple resection but may not effectively enlarge a hypoplastic left ventricular outflow tract.

The transatrial approach for enlarging the left ventricular outflow tract also uses the principle of the modified Konno procedure. The major advantage is that it is simpler and it avoids a right ventriculotomy. The conal enlargement incision starts at the ventricular septal defect patch that already forms part of the outflow tract and is simply extended downward through the area of obstruction and to the left ventricular body; thus patching of the outflow tract is limited to only one area.

We believe that there are a substantial number of

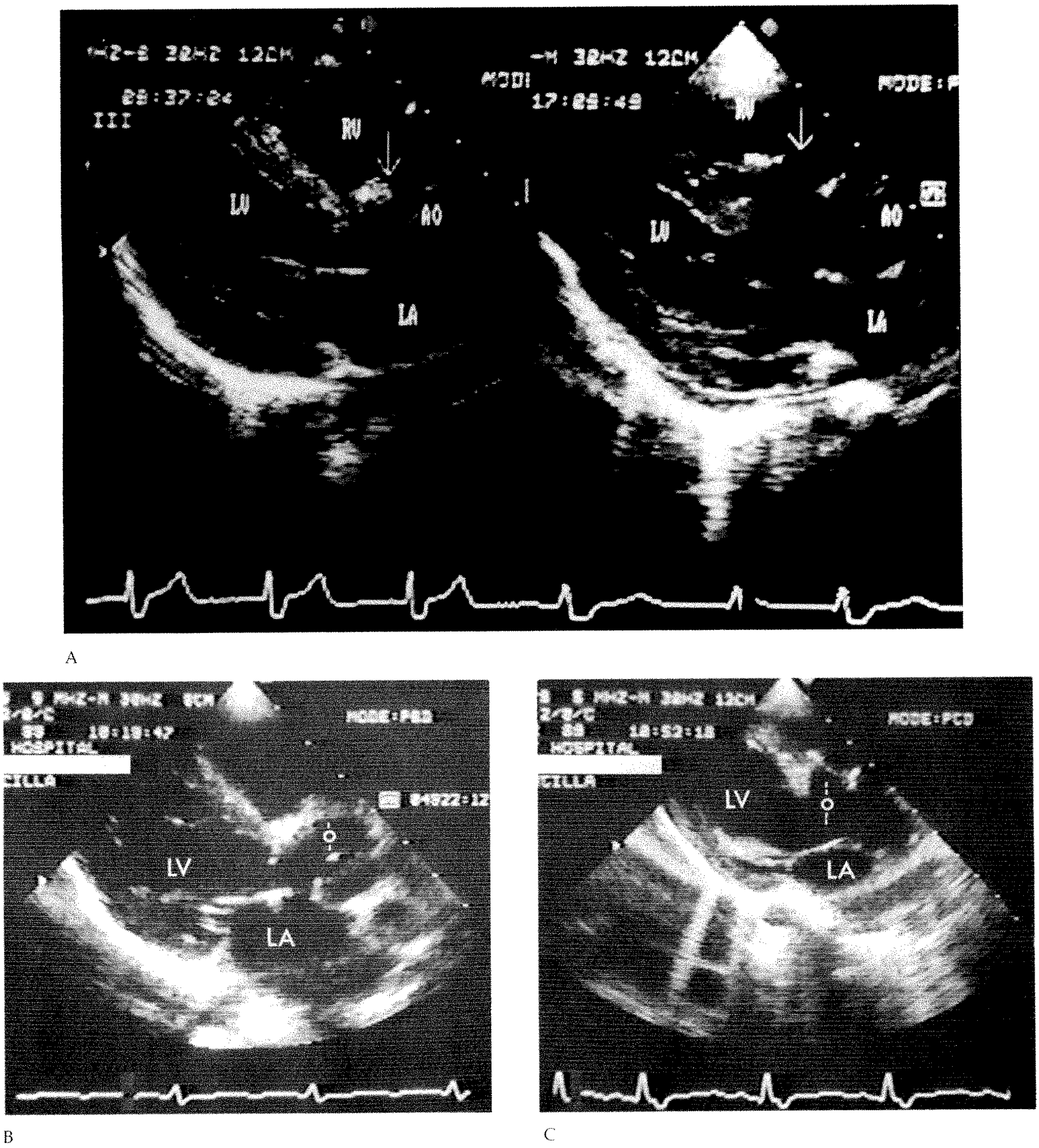

Fig 4. (A) Preoperative echocardiogram (left) of patient 1 showing the narrowed left ventricular outflow tract (arrow)*. Postoperatively (right), the left ventricular outflow tract is wide open. (B) Preoperative and (C) postoperative echocardiograms of patient 3 showing similar appearance of the left ventricular outflow tract (↕).* (AO = *aorta;* LA = *left atrium;* LV = *left ventricle;* RV = *right ventricle.)*

patients who will be suitable for the transatrial approach. Newfeld and colleagues [13] reported a 20% incidence of ventricular septal defect in patients with discrete subvalvular aortic stenosis. The location of the fibromuscular obstruction is often below the ventricular septal defect [9]. Not uncommonly, the outflow obstruction is progressive and becomes hemodynamically significant after closure of the septal defect as illustrated by our 3 patients.

We feel that transatrial enlargement of the left ventricular outflow tract has merits and is a viable option in certain patients with diffuse left ventricular outflow tract obstruction.

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Cefamandole Versus Cefonicid Prophylaxis in Cardiovascular Surgery: A Prospective Study

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We randomized 400 patients who were scheduled for an elective cardiovascular operation involving median sternotomy to receive cefamandole nafate or cefonicid in a prospective double-blind study. Three hundred fifty-seven patients were evaluable for prophylactic efficacy. Chest wound and donor site infections and early prosthetic valve endocarditis occurred more frequently with cefonicid (11 patients, 6.3%) than with cefamandole (4 patients, 2.2%) ($p = 0.05$). Three patients, all in the cefonicid group, required sternal debridement to control postoperative deep wound infections. Twenty-five miscellaneous postoperative infections (urinary tract infection, pneumonia, intravenous site infection, bacteremia, sepsis, *Clostridium difficile* diarrhea) occurred in 16 patients (9.19%) in the cefonicid group and four in 4 patients (2.19%) in the cefamandole group ($p = 0.003$). These data indicate that cefamandole is superior to cefonicid in preventing both surgical wound infections and miscellaneous nonsurgical infections after cardiovascular operations.

(Ann Thorac Surg 1990;49:435–9)

The use of prophylactic antibiotics is an established practice in cardiovascular surgery [1]. The most cost-effective prophylactic regimen has not been determined [2, 3]. First-generation cephalosporins, especially cefazolin sodium, are widely used in prophylaxis in cardiovascular surgery [1, 3]. Kaiser [4], Slama [5], and their colleagues have demonstrated a superiority of second-generation cephalosporins, cefamandole nafate and cefuroxime sodium, over cefazolin. As a result of these studies, cefamandole has become the antibiotic of choice among cardiovascular surgeons in our hospital and elsewhere.

The currently popular prophylactic regimens require additional doses of antibiotics during prolonged surgical procedures and multiple daily doses postoperatively [1, 4]. Cefonicid is a second-generation cephalosporin with a long serum half-life of four to five hours [6]. High levels of cefonicid are achieved in the atrial appendage tissue and pericardial fluid [7]. In a study of patients undergoing coronary artery bypass grafting, Beam and co-workers [8] demonstrated equal surgical infection rates after prophylaxis with cefonicid and cefamandole. Because of the convenience of once-daily administration and the potential cost advantages of cefonicid, we wanted to compare cefonicid and cefamandole for prophylaxis in cardiovascular surgery.

Material and Methods

The study was sponsored by Smith Kline & French Laboratories and approved by the institutional review board. The patients scheduled for an elective cardiovascular procedure involving a median sternotomy were offered participation in the study. Written informed consent was obtained from all participants.

Patients less than 18 years of age, pregnant women, and patients with an active infection, severe allergy to penicillins or cephalosporins, or history of antibiotic therapy within seven days before enrollment were excluded. A patient could participate in the study only once.

The patients showered or bathed with chlorhexidine gluconate soap the night before operation. Also that night, the hair at the operative sites was clipped.

The patients were assigned to one of two prophylactic regimens by a table of random numbers. All randomization was performed by one of us (N.A.). Regimen A consisted of cefamandole, 2 g intravenously at induction of anesthesia, 1 g every two hours during operation, and 1 g every four hours after operation for 72 hours, based on the data of Kaiser and associates [4]. Regimen B included cefonicid, 2 g intravenously at induction of anesthesia and 1 g intravenously every 24 hours after operation for 72 hours, for a total of three postoperative doses, based on the data of Dudley and associates [7]. Patients on regimen B received a placebo (5% dextrose in water) between the doses of cefonicid. The placebo was given at the same time intervals as cefamandole in regimen A so that the investigators remained blinded as to the regimen the patient was receiving. We did not measure serum antibiotic levels in this study.

All antibiotic doses were dispensed in minibags labeled "Moncef." The duration of antibiotic prophylaxis was based on previously published studies and on a widely accepted practice of continuing the antibiotic or antibiotics until removal of all invasive devices (except a peripheral

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intravenous line). However, all antibiotic prophylaxis was stopped at 72 hours regardless of the status of invasive devices. To be evaluable, the patient had to adhere to the protocol for a minimum of 24 hours. The study was conducted between February 1988 and March 1989.

All patients were operated on by one group of cardiovascular surgeons (P.S., O.B.H., E.W.O.). The mediastinum was irrigated with normal saline solution before sternal closure. After the sternum was closed, the chest wound was irrigated with a solution of kanamycin sulfate in normal saline solution (1 g/L of saline solution).

A chest wound or donor site was considered infected if purulence was observed during daily examination by one of us and confirmed by another. Patients were monitored prospectively during hospitalization for the presence of nonsurgical wound infections (eg, bacteremia, pneumonia, urinary tract infection, intravenous site infection, *Clostridium difficile* diarrhea) by us and the infection control nurses. Standard definitions of infections (Centers for Disease Control) were used. Sepsis was defined as an acute febrile episode with negative cultures that was treated with antibiotics and for which no other specific cause was found. All patients were telephoned 30 days after discharge and queried about signs and symptoms of wound infection and use of antibiotics.

The following variables were recorded prospectively for all patients: age and sex; name of the operating surgeon; duration of hospitalization before operation; smoking history; presence of obesity (greater than 20% over ideal body weight), diabetes mellitus, hypertension, and renal insufficiency (serum creatinine level greater than 2 mg/dL); use of internal mammary artery in coronary artery bypass grafting; perfusion time; and cross-clamp time.

According to the protocol design, after the first 400 patients were enrolled into the study, the infection rate for the two regimens, identified with a letter code, was calculated. The study was ended and the code broken when a significant difference was detected between the two regimens. All statistical tests for association of frequency were performed by χ^2 analysis or by Fisher's exact test when expected frequencies were less than five.

Results

Forty-three of the 400 patients enrolled in the study were excluded. Those excluded were evenly distributed between the two groups. The reasons for exclusion included cancellation of operation, administration of an antibiotic not covered in the study, or death unrelated to infection during the study period. Three hundred fifty-seven patients were evaluable for prophylactic efficacy. One hundred eighty-three received cefamandole and 174, cefonicid. We observed no antibiotic side effects in our study.

An analysis of surgeon-specific infection rates revealed no significant differences. Demographic and risk factors did not differ between the groups.

The rates of surgical wound infection and early prosthetic valve endocarditis detected during the initial hospitalization or resulting in hospital readmission and surgical procedures are listed in Table 1. One chest and one donor site infection in the cefamandole group and one chest and two donor site infections in the cefonicid group were detected after discharge of the patients and resulted in readmission; they are included in Table 1. There were significantly more surgical wound infections in the cefonicid group, and 4 patients required major surgical procedures for control of infection (sternal debridement with pectoral muscle flaps, prosthetic valve replacement). The only death, possibly related to infection, occurred in the cefonicid group (deep sternal wound infection and purulent pericarditis secondary to *Staphylococcus aureus* with a postoperative aortic hemorrhage). One patient in the cefamandole group had chest wound debridement. All of the patients with infection received local wound care and intravenous antibiotics.

The microbiological isolates from the surgical wound infections are listed in Table 2. Although the small number of infections prevents any conclusions about the relative frequency of infections with specific microorgan-

Table 1. Surgical Wound Infections and Early Prosthetic Valve Endocarditis[a]

Infection	Cefamandole	Cefonicid
Chest wound	2 (1, debridement)	5 (3, sternal debridement)
Donor site	2	5
Endocarditis	0	1 (valve replacement)
Total[b]	4/183 (2.2%)	11/174 (6.3%)

[a] All were diagnosed during initial hospitalization or resulted in readmission. [b] Significance: $p < 0.05$ between the two groups.

Table 2. Microbiology of Surgical Infections

Antibiotic	Isolates
Cefamandole	
Chest	Methicillin-resistant *Staphylococcus epidermidis*
Chest	None
Leg	*Enterobacter cloacae;* enterococcus
Leg	*Pseudomonas aeruginosa;* methicillin-resistant *Staphylococcus epidermidis*
Cefonicid	
Prosthetic valve endocarditis (mitral)	Methicillin-resistant *Staphylococcus epidermidis*
Chest	*Staphylococcus aureus*
Chest	Methicillin-resistant *Staphylococcus epidermidis*
Chest	None
Chest	*Staphylococcus epidermidis*
Chest	Methicillin-resistant *Staphylococcus aureus*
Leg	None
Leg	Methicillin-resistant *Staphylococcus aureus*
Leg	*Enterobacter cloacae;* enterococcus
Leg	None
Leg	None

Table 3. Nonsurgical Infections

Site of Infection	Cefamandole	Cefonicid
Lower respiratory tract	2	7
Urinary tract	2	9
Bacteremia	0	4
Sepsis	0	2
Intravenous site	0	1
Clostridium difficile diarrhea	0	2
Total[a]	4/183 (2.19%)	25/174 (14.37%)

[a] Significance: $p < 0.001$, number of infections between the two groups.

isms, *S aureus* was isolated only from the cefonicid group (n = 3). Five patients, 4 in the cefonicid group, had no microorganisms isolated on culture. We did not test the isolates against the study antibiotics, but methicillin-resistant staphylococci, enterococci, and *Pseudomonas aeruginosa* usually are resistant to both cefamandole and cefonicid.

Infections that occurred after the patient was discharged and were reported on a 30-day telephone survey but did not require readmission to the hospital are as follows: leg infection, 5 patients in the cefamandole group and 3 in the cefonicid group; chest infection, 2 in the cefonicid group. These were superficial infections that were managed by each patient's private physician with oral antibiotics and local care. Cultures usually were not performed. We chose not to include these infections in the calculations of surgical wound infection rates for the following reasons: the infections had minimal morbidity, did not require readmission or intravenous antibiotics, and were not confirmed microbiologically.

The nonsurgical infections detected during the initial hospitalization are listed in Table 3. Four patients in the cefamandole group had four nonsurgical infections, and 25 nonsurgical infections occurred in 16 patients in the cefonicid group ($p = 0.003$ for patients with infection). The microbiological isolates from nonsurgical infections are listed in Table 4. Two patients in the cefamandole group had a culture-negative pneumonia. The difference between the groups in nonsurgical infections is highly significant and resulted in frequent use of therapeutic antibiotics (not presented).

Comment

The value of antibiotic prophylaxis in cardiovascular surgery has not been proved conclusively, but because of the high morbidity and mortality associated with sternal wound infections, mediastinitis, and prosthetic valve endocarditis, placebo-controlled trials are unlikely [2, 9]. Furthermore, it is possible to infer the value of prophylaxis from comparative antibiotic trials because some antibiotics result in lower infection rates than others, and it is very unlikely that less-effective antibiotics cause infections [4, 5, 9, 10].

Cardiovascular surgeons are, therefore, faced with a choice of the best and most cost-effective prophylactic agents. The majority of surgical wound infections in cardiovascular surgery are caused by staphylococci (*S aureus* and *Staphylococcus epidermidis*), streptococci, and gram-negative aerobic rods [11]. Until recently, first-generation cephalosporins (cephalothin sodium, cephapirin sodium, cefazolin) were the most popular agents. Several recent studies [4, 5, 12] showed a superiority of second-generation cephalosporins, cefuroxime and especially cefamandole, over cefazolin in cardiovascular surgery, although these findings have not been confirmed in other studies [13, 14].

Several explanations have been offered for these results. Methicillin-resistant staphylococci (*S epidermidis* and *S aureus*) have increased in recent years and, as in our study, account for a high percentage of postoperative isolates [15]. Cefamandole is the most active of all cephalosporins in vitro against methicillin-resistant staphylococci and has been successfully used in clinical infections with methicillin-resistant *S epidermidis* and *S aureus* [15–18]. In our hospital, 25% of *S aureus* and 50% of *S epidermidis* infections are methicillin resistant. Kernodle and Kaiser [19] reported that surgical isolates of *S aureus* from St. Thomas Hospital in Nashville, TN, produced a β-lactamase capable of inactivating cefazolin but not cefamandole. These isolates were from the patients given prophylactic cefazolin. The activity of this β-lactamase against cefonicid has not been determined. Only one surgical wound infection with *S aureus* occurred in 814 patients given cefamandole in the studies by Kaiser and colleagues [4], Slama and co-workers [5], and ourselves [present study] and none in 705 patients given high-dose cefamandole prophylaxis [4, present study]. Cefamandole appears to be clearly superior to cefazolin in preventing cardiovascular surgical wound infections with *S aureus* [15].

Cefamandole does have a relatively short half-life (0.8 hour) and has to be administered every four hours (and more frequently intraoperatively) to maintain adequate trough levels [4].

Two second-generation cephalosporins with a prolonged half-life, ceforanide (half-life = three hours) and cefonicid (half-life = four to five hours), offer the conve-

Table 4. Microbiology of Nonsurgical Infections

Isolate	Cefamandole	Cefonicid
Staphylococcus aureus	0	4
Staphylococcus epidermidis	0	3
Methicillin-resistant *Staphylococcus aureus*	0	1
Enterococci	0	4
Escherichia coli	2	2
Enterobacter cloacae	0	2
Pseudomonas aeruginosa	0	4
Miscellaneous	0	10[a]
None	2	0

[a] They included the following: *Klebsiella pneumoniae*, *Candida albicans*, and *Clostridium difficile*, 2 patients each; and *Acinetobacter anitratus*, *Branhamella cattarrhalis*, group F streptococci, and viridans streptococci, 1 patient each.

nience and potential cost advantage of less frequent administration [10, 20]. In a study published in 1984 [10], ceforanide was shown to be superior to cephalothin in cardiovascular surgical prophylaxis. In 1987, Beam and colleagues [8] reported that the infection rate was similar in patients given cefonicid and cefamandole. A relatively small number of patients was studied, raising the question of a type II error.

Our study was designed to compare the effectiveness of cefamandole and cefonicid for prophylaxis in cardiovascular surgery. In a 1986 review of antimicrobial prophylaxis in surgery, Kaiser [1] listed the criteria for designing studies of antimicrobial prophylaxis of surgical wound infections. The criteria included the following: prospective, randomized, double-blind design; written definitions of surgical wound infection; comparability of host risk factors; equal distribution of operative procedures; appropriate choice of antimicrobial agent or agents for the expected pathogens; adequate dosing throughout the operative procedure; controlled use of antibiotics or antiseptics not in the study; the use of antibiotics with a minimal risk of toxic or allergic reactions; sufficient numbers of patients to demonstrate significant differences (or lack thereof); and comparison of costs. All of these except the cost analysis were included in our study. The study revealed that the patients given cefamandole had significantly fewer surgical wound infections and nonsurgical infections than the cefonicid group. Therefore, we thought the cost analysis would be of secondary importance.

Several possible explanations can be offered for these results. In vitro activity of cefonicid against staphylococci, both methicillin susceptible and methicillin resistant, is inferior to that of cefamandole, especially when tested with human serum [16, 20, 21]. Cefonicid is highly protein bound (98%) [20]. Serum levels of free (unbound) cefonicid during the second half of a 24-hour dosing interval may be too low to achieve adequate tissue levels [22]. Serum and tissue antibiotic levels during operation are known to be important in preventing surgical wound infections [23, 24]. Low serum levels of free antibiotic can also result in suboptimal serum bactericidal activity, as reported by Chambers and colleagues [25] in patients failing once-daily cefonicid therapy for *S aureus* endocarditis.

The high frequency of nonsurgical infections in patients given cefonicid is disturbing. These infections resulted in major morbidity and necessitated additional systemic antibiotic therapy. Although not specifically examined, the cost of hospitalization was undoubtedly higher in patients with infection. Krieger and associates [26] showed that urinary tract infections can result in postoperative surgical wound infections. We observed no such occurrence in our study. The design of the study does not allow us to determine whether cefonicid was less effective than cefamandole in preventing postsurgical infections or, although very unlikely, actually predisposed the patients to infections. A placebo group would have been needed to determine this.

Flynn and co-authors [27] reported increased postoperative *Enterobacter* infections in cardiovascular surgical patients and related it to cefazolin prophylaxis. Kernodle and associates [28] demonstrated the emergence of methicillin-resistant coagulase-negative staphylococci in cardiac surgical patients given antibiotic prophylaxis. Only placebo-controlled studies can answer the question of whether antibiotic prophylaxis in cardiovascular surgery can actually predispose the patient to postoperative infections. *Clostridium difficile* diarrhea developed in 2 patients given cefonicid. Cannon and colleagues [29] reported *C difficile* diarrhea after perioperative antibiotic prophylaxis in orthopedic surgery.

Surveillance after discharge has been emphasized recently [30]. We conducted a telephone survey 30 days after discharge and identified 10 patients with minor wound infections not necessitating rehospitalization or intravenous antibiotics. Our survey did not uncover any patients with serious infections who were readmitted to another hospital. All such patients returned to our hospital for care. Hospitals with different referral patterns may find postdischarge surveillance to be of greater value.

In conclusion, we found that cefamandole is superior to cefonicid in preventing surgical wound infections and nonsurgical infections in patients after cardiovascular operations. Future studies of antibiotic prophylaxis in surgery should monitor both surgical wound and nonsurgical postoperative infections.

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Low Activated Coagulation Time During Cardiopulmonary Bypass Does Not Increase Postoperative Bleeding

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The activated coagulation time (ACT) is widely used to monitor adequacy of anticoagulation during cardiopulmonary bypass despite absence of data establishing an ACT below which adverse outcomes occur. For anticoagulation before cardiopulmonary bypass, we administered a single dose of heparin (300 U/kg) to 193 patients and measured ACT and heparin levels at intervals after administration. No additional heparin was administered to any patient. Clot formation in the cardiopulmonary bypass circuit and excessive postoperative chest tube drainage were considered outcomes indicating inadequate anticoagulation. Cardiopulmonary bypass averaged 59 ± 23 minutes (range, 30 to 138 minutes). Activated coagulation time values at every sampling period were normally distributed. In 51 patients (26.4%) ACT values were less than 400 seconds, including 4 less than 300 seconds, at some sampling time after heparinization. Patients with low ACT values did not bleed more postoperatively than those with high ACT values, nor was bleeding related to heparin level. No clots were found in any perfusion circuit. We conclude that a minimum ACT value for adequacy of heparinization is not yet defined but that it is less than 400 seconds.

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Heparin is administered to patients undergoing open heart operations to prevent clot formation during cardiopulmonary bypass (CPB). In the absence of clot, inadequate heparin has been postulated to increase postoperative bleeding by subclinical consumption of activated clotting factors during CPB [1, 2]. In practice, a heparinized activated coagulation time (ACT) in excess of some certain arbitrary value is believed to assure adequacy of heparinization by preventing clot formation and excessive postoperative bleeding. Although several minimum ACT values have been proposed [1–3], a value below which patients experience this adverse effect has never been defined. Despite this, a minimum ACT value has become the standard of care in many institutions.

For more than 20 years we have administered an empirical single dose of heparin (300 U/kg) before CPB without routine measurement of ACT or requirement of a minimum ACT value and failed to observe clot in the oxygenator during perfusions lasting as long as two hours. This clinical practice provided the opportunity to relate heparinized ACT values to evidence of inadequate anticoagulation in terms of postoperative bleeding. We specifically sought patients with heparinized ACT values less than 400 seconds, a commonly accepted minimum value, and occurrence of clot in the CPB circuit or excessive postoperative bleeding as consequences of inadequate anticoagulation [1–8]. We also measured simultaneous heparin levels and ACT values to determine if low heparin levels (less than 2 U/mL) were associated with adverse outcomes.

Material and Methods

All patients scheduled for elective cardiac operations requiring CPB were eligible for study. Patients with abnormal preoperative coagulation tests and those receiving heparin within 12 hours of operation were excluded. Patients taking antiplatelet medications were not excluded. With institutional review board approval, 202 patients were studied. The group included 126 patients undergoing coronary artery bypass operations, including 15 patients with previous cardiac operations, and 76 patients undergoing open cardiac chamber operations with or without coronary artery bypass grafting, including 11 patients with previous cardiac operations.

Before aortic cannulation each patient received 300 U/kg of heparin (pork intestine) intravenously. The extracorporeal circuit was primed with 20 mL/kg of heparinized (2,500 U/L) 5% dextrose in lactated Ringer's solution. Some patients received additional crystalloid without heparin to maintain a safe level in the venous reservoir. Cardiotomy suction reservoirs included 40-μm depth filters. No arterial filters were used. With onset of CPB, all patients were cooled to 28° to 30°C and then warmed to 37°C before separation from CPB. No patient received additional heparin. After CPB, patients received approximately 1.5 mg of protamine for each 100 U of intravenously administered heparin. The endpoint for protamine administration was the appearance of visible firm clots in the surgical field. Additional protamine (50 to 100 mg) was administered initially to all patients in whom firm

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clots failed to develop or who appeared to bleed excessively before other therapy was instituted.

Activated coagulation time was measured four times: before heparin ("preheparin"), five minutes after heparin administration but before start of CPB ("postheparin"), five minutes after start of CPB during hypothermia ("early CPB"), and at normothermia before the end of CPB ("late CPB"). Heparin level was assayed at identical times in 117 patients. Activated coagulation time was assessed in duplicate on a single Hemochron dual-chamber apparatus (International Technidyne Corp, Metuchen, NJ), and the mean value was recorded. Heparin levels were determined on a Hepcon System Four protamine titration system (Hemotec, Inc, Englewood, CO) with cartridges in the range of 2.5 to 4.0 U/mL. When the initial level was 2.5 U/mL, the determination was repeated with a cartridge in the range of 0.5 to 2.0 U/mL. When the initial level was 4.0 U/mL, the test was not repeated. The surgeon, anesthesiologist, and perfusionist participating in the operation were unaware of ACT and heparin values. Postoperative blood loss was measured as cumulative chest tube output (CTO) during the first 24 hours after arrival in the intensive care unit. Blood loss during operation was not included in CTO. The perfusionist monitored the CPB circuit continuously during CPB and at termination of CPB carefully examined the oxygenator, arterial and venous tubing, and the cardiotomy filter and reservoir for clot.

Three patients died within 24 hours of operation of causes unrelated to blood loss. Six additional patients were returned to the operating room for reexploration and control of postoperative bleeding. A surgical cause of bleeding was found in each patient. Activated coagulation time was greater than 400 seconds and heparin level was greater than 2 U/mL at all measurement times in these patients. These 9 patients were excluded because of incomplete blood loss data.

Based on postheparin ACT, patients were grouped at 50-second ACT intervals ranging from 250 to 750 seconds. Mean CTO for each ACT group was compared for trends and for low versus high ACT groupings. Similar comparisons were made using the percentage of patients in each group with CTO greater than 1,000 mL and CTO greater than 1,500 mL as outcome measures. These analyses were repeated using ACT values of early CPB, late CPB, percentage of increase from preheparin baseline, and lowest heparin level.

Continuous data are presented as mean ± standard deviation. Two-tailed Student's t tests for paired data were used to determine the significance of differences between ACT before and during CPB. Student's t tests for unpaired data were used to determine significant differences between CTOs. Statistical inference on proportions was obtained with χ^2 test and, when necessary, the Yates continuity correction was applied. Normal distribution was confirmed using normal probability graph paper. Because our heparin assay determined blood level to the nearest 0.5 U/mL, assay values were considered discontinuous variables and the statistical tests described were not applied.

Table 1. Mean Activated Coagulation Times Before and During Cardiopulmonary Bypass in 193 Patients

Sampling Time	Mean ACT ± SD (s)	Range (s)
Preheparin	134 ± 14	95–183
Postheparin	525 ± 118[a]	239–999
Early CPB	573 ± 144[b]	288–999
Late CPB	513 ± 125[a]	234–999

[a] Significantly different from preheparin values ($p < 0.01$). [b] Significantly greater than both postheparin and late CPB ($p < 0.05$).

ACT = activated coagulation time; CPB = cardiopulmonary bypass; SD = standard deviation.

Results

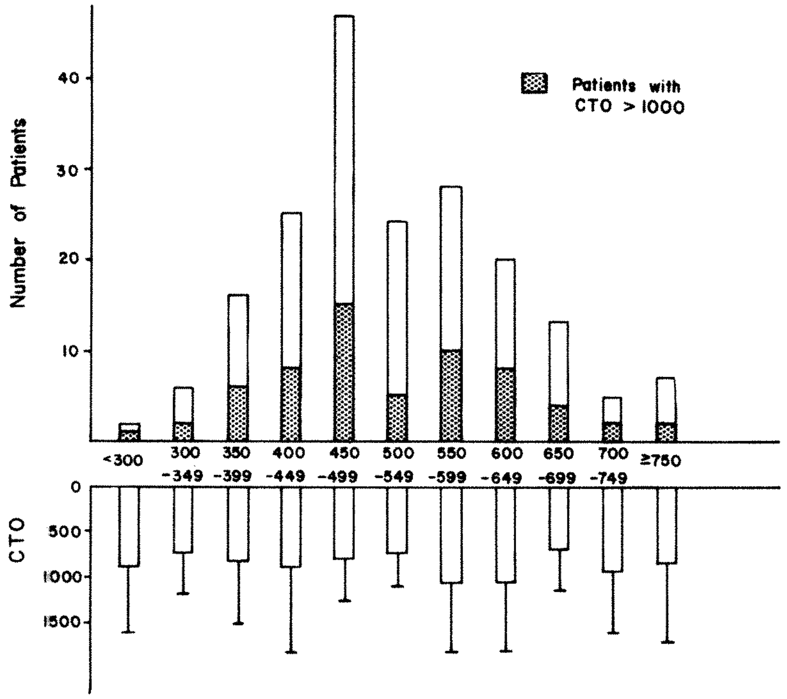
Activated coagulation time was determined at all four sampling times in 193 patients with simultaneous heparin levels in 117 patients. Preheparin ACT was 134 ± 14 seconds (range, 95 to 183 seconds) (Table 1), similar to mean control ACT values before CPB ranging from 130 to 135 seconds reported by other investigators [9–11]. Administration of 300 U/kg of heparin increased mean ACT fourfold ($p < 0.01$), with values fitting a normal distribution curve about a mean of 525 seconds (Fig 1). A small additional increase in ACT followed the onset of CPB, and ACT decreased to the early CPB level by the end of bypass ($p < 0.05$) (Table 1). Mean duration of CPB was 59 ± 23 minutes (range, 15 to 138 minutes).

In 24 patients (12%) postheparin ACT was less than 400 seconds, including 2 patients in whom it was less than 300 seconds (239 and 261 seconds) (Table 2). In 13 patients (7%) early CPB ACT was less than 400 seconds, including 1 with 288 seconds. In 30 patients (15%) late CPB ACT was less than 400 seconds, including 2 with values of 234 and 299 seconds. Eight patients (4%) had ACT values less than 400 seconds at both early and late CPB sampling times. Patients with postheparin values less than 400 seconds had a greater increase in ACT after onset of CPB (113 ± 155 seconds) than those with postheparin ACT greater than 400 seconds (38 ± 105 seconds) ($p < 0.05$).

Mean CTO for all patients was 887 ± 620 mL (range, 50 to 3,950 mL). Mean CTO did not differ significantly between coronary bypass and open chamber operations, between first operations and reoperations, or between the 31 patients taking antiplatelet medications and the 158 patients not taking such medications. Because of the large variation of CTO values, these groups were compared in terms of percentage of patients with CTO greater than 1,000 mL and greater than 1,500 mL as measures of excessive bleeding. No differences between groups were apparent. In addition, mean CTO of 17 patients with CPB less than 30 minutes did not differ from that of 15 patients with CPB longer than 90 minutes.

Chest tube output, both mean and frequency of blood loss greater than 1,000 and 1,500 mL, did not correlate with postheparin ACT (Table 2 and Fig 1), nor did it correlate with early or late CPB ACT values or with percentage of increase in postheparin ACT over preheparin values. When analysis was limited to patients under-

Fig 1. Distribution of 193 patients by postheparin activated coagulation time values in 50-second increments and chest tube output (CTO) in each of these groups. Bottom clear bars *represent mean chest tube output in milliliters ± standard deviation.* Shaded bars *represent number of patients with chest tube output greater than 1,000 mL. Activated coagulation time values were normally distributed.*



going primary coronary bypass (n = 117), CTO did not correlate with high or low ACT values. In 4 patients ACT remained less than 400 seconds at all sampling times and their CTO did not differ from that of patients with higher ACT.

Postheparin heparin levels ranged from 2.0 to 4.0 U/mL (Table 3), with 65% of patients having a level greater than 3.0 U/mL. Heparin level decreased markedly with onset of CPB, with only 8% of patients having a level greater than 3.0 U/mL during the same period in which ACT values increased significantly. At late CPB 12% of patients had levels greater than 3.0 U/mL. No patient had a heparin level less than 2.0 U/mL at any sampling time. Lowest heparin level did not correlate with CTO or with frequency of excessive CTO. Activated coagulation time did not correlate with heparin level at any sampling time.

No clot was found in any extracorporeal circuit during or after CPB. No cardiotomy filter required replacement.

Comment

The concept of a minimal ACT ensuring adequacy of heparinization for CPB was based on the work of Young and colleagues [1], who detected elevated fibrin monomer in the plasma of 6 of 9 monkeys after 30 minutes of CPB. In 5 of these 6 monkeys, the initial ACT during CPB was less than 400 seconds. Postoperative bleeding was not monitored. Young and colleagues [1] also reported no elevated fibrin monomer and no excessive postoperative bleeding in 5 children who received sufficient heparin to maintain ACT greater than 400 seconds before and during CPB. They concluded that heparinized ACT values less

Table 2. Relation Between Activated Coagulation Time During Cardiopulmonary Bypass and Postoperative Blood Loss

Sampling Time	ACT Range (s)	Patients (n)	Mean CTO ± SD (mL)	CTO >1,000 mL (% of Patients)	CTO >1,500 mL (% of Patients)
Postheparin	<400	24	854 ± 636	33	20
	400–600	122	887 ± 621	32	11
	>600	47	912 ± 619	36	15
Early CPB	<400	13	712 ± 386	23	4
	400–600	102	887 ± 660	30	11
	>600	78	917 ± 599	37	17
Late CPB	<400	30	738 ± 368	23	4
	400–600	124	913 ± 635	34	15
	>600	39	920 ± 718	36	13

ACT = activated coagulation time; CPB = cardiopulmonary bypass; CTO = cumulative chest tube output; SD = standard deviation.

Table 3. Heparin Levels After 300 U/kg of Heparin Intravenously in 117 Patients During Cardiopulmonary Bypass

Heparin Level (U/mL)	Postheparin (% of Patients)	Early CPB (% of Patients)	Late CPB (% of Patients)
2.0	3	9	22
2.5	6	46	39
3.0	26	37	27
3.5	46	6	10
4.0	19	2	2

CPB = cardiopulmonary bypass.

than 400 seconds were associated with activation of the coagulation cascade. Their observations have not been subsequently confirmed in any animal model or in humans. Nonetheless, the ACT value of 400 seconds has been widely accepted as the lower safe limit for CPB in humans. Our established practice of administration of a single heparin dose for CPB provided an opportunity for a limited test of the validity of this value in a clinical setting.

Administration of a single dose of heparin of 300 U/kg increased mean ACT fourfold. Activated coagulation time values increased further with onset of CPB, probably because of hemodilution and hypothermia [12], and returned to the initial mean postheparin value by the end of CPB, probably secondary to restoration of normothermia and hemoconcentration by diuresis during CPB. Activated coagulation time values at each sampling time were normally distributed, as expected from any measure of response to a single uniform heparin dose. We identified 51 patients with ACT less than 400 seconds, including 4 patients with ACT less than 300 seconds at some time during CPB who did not form clot in the oxygenator and whose postoperative bleeding was not different from that of patients with higher ACT. Data of these 51 patients, 26.4% of all patients, failed to support the 400-second minimum ACT value for adequacy of heparinization.

As reported by other investigators [13, 14] and in our study, volume of postoperative bleeding after operations requiring CPB varied widely. This bleeding can be attributed not only to the postulated depletion of activated coagulation factors but also to platelet dysfunction, hyperfibrinolysis, and surgical causes [15]. As a better index of adequacy of heparinization during CPB, investigators recently measured fibrinopeptide A (FPA) levels during operations requiring CPB with ACT maintained at more than 400 seconds. If heparin completely prevented thrombin formation, then no FPA, a byproduct of fibrinogen conversion to fibrin, should be detectable during CPB. Davies and co-workers [16] found that FPA levels decreased at the start of CPB and were less but still present at the end of bypass. Gravlee and associates [17] and Mammen and colleagues [18] confirmed this pattern using a variety of heparin regimens that maintained ACT at more than 400 seconds. Gravlee and associates found no correlation between FPA levels during CPB and postoperative bleeding, between FPA and ACT during CPB, or between FPA levels during CPB and postoperative abnormalities in prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen levels, or fibrin degradation products. Measurable levels of FPA are present during CPB, but high FPA levels do not identify patients who will bleed excessively after operation.

Some data of other investigators support the sufficiency of a single heparin dose of 300 U/kg. Culliford and colleagues [12] managed 28 patients with this dose, followed by 100 U/kg each hour of CPB thereafter. Despite ACT values as low as 286 seconds during CPB, neither clot formation nor fibrin accumulation in arterial filters by electron microscopy were observed in any patient. Dauchot and co-workers [9] managed 22 patients undergoing approximately 90 minutes of CPB with an initial heparin dose of 150 U/kg, followed by 3,000 to 5,000 U whenever ACT values were less than 270 seconds. They observed but did not treat 26 instances of ACT less than 300 seconds without abnormal postoperative bleeding. Our data from 193 patients support the sufficiency of 300 U/kg of heparin for at least 1 hour of CPB independent of ACT values.

Heparin levels did not correlate with ACT or CTO at any sampling time. When ACT increased at the onset of CPB, heparin levels decreased and continued to decrease while mean ACT remained high. No patient had a heparin level less than 2.0 U/mL at any time as compared with the wide range of observed ACT values. A heparin level of 2.0 U/mL may be a more reliable indicator than ACT of intravascular administration of heparin and of adequacy of heparinization for perfusions lasting as long as two hours.

In summary, our data demonstrate that 300 U/kg of heparin provides safe anticoagulation for at least one hour and possibly two hours of CPB. Monitoring of ACT or heparin levels with this regimen would not have contributed to the quality of care of these patients. Neither ACT nor heparin values identified patients who bled excessively after operation or formed clot during CPB. We conclude that no established minimum ACT value yet defines adequacy of heparinization during CPB.

Addendum

Since submission of this report, we continued to monitor postheparin ACT to discover other patients with initial values less than 400 seconds. We identified 22 additional patients whose postheparin ACT ranged from 330 to 397 seconds. Their mean CTO was 944 ± 687 mL, with 32% and 19% bleeding more than 1,000 and 1,500 mL, respectively. These data are strikingly similar to those shown in Table 2. Four of the 22 patients had ACT values less than 400 seconds at all three sampling times and their CTO was 920 ± 475 mL. Six of the 22 patients had late CPB ACT values ranging between 227 and 292 seconds and had CTO of 888 ± 560 mL after operation. These additional data strengthen our conclusion that the minimum ACT value for adequacy of heparinization is clearly less than 400 seconds.

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INVITED COMMENTARY

Our ability to quantify phenomena gives us a sense of security. The current report by Metz and Keats properly destroys that sense of security, at least in the use of ACT to monitor heparin use during cardiopulmonary bypass.

Using a standard dose of heparin before the institution of CPB, they found no correlation of postoperative bleeding with the intraoperative ACT or heparin level. Further, they found no correlation between heparin levels and ACT. No gross evidence of clot in the perfusion circuits was found at the completion of any operation. The patients with an intraoperative ACT of less than 400 seconds had no more chest tube output than those with ACTs of greater than 400 seconds.

The report provokes thought and comment more for what it does not say than for what it does. Metz and Keats did not answer the question of how much heparin is necessary. They did not answer the question of how often heparin should be readministered—most of their CPB times were brief. They did not perform any blood assays for activation of the clotting cascade and the attendant diminution of clotting factors. And although they demonstrated that the ACT during bypass did not correlate with the amount of postoperative bleeding, they did not investigate another important variable affecting bleeding: the adequacy of heparin reversal. Without confirmation of postoperative heparin reversal, conclusions drawn about another variable (intraoperative ACT) from the amount of bleeding must be suspect.

Cardiopulmonary bypass has been shown to trigger the clotting cascade and to lead to fibrinolysis. At some point of decreasing anticoagulation, this phenomenon presumably increases and can be expected to lead to deleterious consequences, especially with longer CPB times. The practicing cardiac surgeon needs to know the point at which this occurs, not just that a lower ACT (we do not know how much lower from this report) does not cause increased bleeding.

Nevertheless, this report is a valuable one. It calls into question our regard of the ACT as an icon, and should stimulate further studies—perhaps by Drs Metz and Keats—in the underresearched area of heparin use during CPB.

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Futility of Pericardiectomy for Postirradiation Constrictive Pericarditis?

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Two patients underwent pericardiectomy for postirradiation constrictive pericarditis. Both had received radiotherapy (more than 6,000 rads) for treatment of Hodgkin's disease 17 (patient 2) and 20 years (patient 1) earlier. At the time of operation, the patients were in New York Heart Association functional class III-IV or IV. Preoperative catheterization showed the following pressures for patients 1 and 2, respectively: right atrial, 30 and 14 mm Hg; right ventricular end-diastolic, 28 and 14 mm Hg; wedge, 29 and 13 mm Hg; and left ventricular end-diastolic, 27 and 14 mm Hg. Complete epicardiectomy and pericardiectomy was attempted in both patients. However, hospital mortality was 100%; patient 1 died of multiorgan failure after six days, and patient 2 died of biventricular failure after 3 months. A review of the literature revealed 44 cases of pericardiectomy for postirradiation constrictive pericarditis and a late survival rate of less than 50%. The poor results in these patients compared with patients having pericardiectomy for other reasons seem to be due mainly to the various kinds of radiation-induced damage to the heart as a whole, including untimely coronary artery disease, myocardial fibrosis, atrioventricular conduction disturbances, and valve dysfunction, with the result that complete relief by epicardiectomy and pericardiectomy may not be technically feasible.

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Radiotherapy is effective for the treatment of some malignancies, such as Hodgkin's disease, and today is widely used clinically. However, it has been shown that irradiation can cause extensive damage to the heart and pericardium [1–7]. In 1987, 2 patients with severe postirradiation constrictive pericarditis were operated on in our institution, and the results were disappointing. The indications and results of pericardiectomy in these patients are analyzed and compared with those in a series of 44 pericardiectomies for postirradiation constrictive pericarditis collected from the literature.

Case Histories

Patient 1

A 38-year-old man was referred for pericardiectomy for postirradiation constrictive pericarditis 20 years after discovery of a mass in the anterior mediastinum. In 1967, the results of biopsy were Hodgkin's disease of the nodular sclerosing type, and a course of radiotherapy was given. In 1968, a second series of radiotherapy was given to stabilize the result. The patient had two relapses, one in 1970 and one in 1975, and both times, remission was achieved with additional radiotherapy. The total dose of radiation applied to the mediastinum was in excess of 8,000 rads. Thereafter, the patient was well until 1985.

Increasing dyspnea occurred in December 1985, and a chest roentgenogram showed a large pleural effusion on the right side. Computed tomographic scanning, magnetic resonance imaging, and echocardiography revealed a severely thickened pericardium (greater than 3 cm). Despite intensive use of diuretic agents and repeated thoracentesis (up to two to three times per week), the condition of the patient continued to deteriorate and his New York Heart Association functional status was assessed as class IV. The diagnosis of constrictive pericarditis was confirmed by cardiac catheterization in February 1987 (Table 1). Furthermore, the coronary angiogram showed diffuse changes in the coronary arteries.

Pericardiectomy for postirradiation constrictive pericarditis was performed in March 1987 through a midline sternum-splitting incision. The mediastinum was densely fibrotic, and pericardiectomy proved to be extremely difficult; however, it was possible to excise the anterior pericardium and the epicardium from the great vessels to both phrenic nerves including the diaphragmatic surface. The posterior cardiac wall could be freed only by sharp dissection. As the right lung was partially restricted by a fibrous membrane, decortication of that lung was attempted but had to be abandoned because the inflammatory adhesions bled severely. Cardiac index, assessed by thermodilution, increased from 1.59 L/min/m^2 (central venous pressure, 22 mm Hg; pulmonary capillary wedge pressure, 24 mm Hg; arterial pressure, 69 mm Hg) before sternotomy to 2.05 L/min/m^2 (central venous pressure, 13 mm Hg; pulmonary capillary wedge pressure, 20 mm Hg; arterial pressure, 67 mm Hg) after sternal closure.

In the early postoperative period, the hemodynamic condition of the patient was stabilized by positive inotropic medication combined with vasodilators. However, massive heart failure occurred after two days, and he died of multiorgan failure six days after operation despite all resuscitative measures including the intraaortic balloon pump.

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Table 1. Cardiac Catheterization Data

Variable	Patient 1	Patient 2
Right atrial pressures (mm Hg)		
A wave	30	14
V wave	28	14
Mean	27	12
Right ventricular pressures (mm Hg)		
Systolic	50	32
End-diastolic	28	14
Pulmonary capillary wedge pressure (mm Hg)	29	13
Left atrial pressures (mm Hg)		
A wave	. . .	17
V wave	. . .	17
Mean	. . .	14
Left ventricular pressures (mm Hg)		
Systolic	95	85
End-diastolic	27	14
Cardiac index (L/min/m^3)	2.1	3.2
Left ventricular ejection fraction (%)	66	74
Mean of right atrial (mean), right ventricular (end-diastolic), wedge, and left ventricular (end-diastolic) pressures[a]	28 ± 1	13 ± 1

[a] Data are shown ± the standard deviation in millimeters of mercury.

Microscopic analysis of the removed epicardium and pericardium revealed sclerotic, thickened scar tissue with signs of unspecific, moderate, chronic inflammation without calcifications, findings quite compatible with an actinic origin. There was no evidence of remaining Hodgkin's disease. Postmortem examination was refused by the patient's family.

Patient 2

This 38-year-old patient was referred for pericardiectomy for postirradiation constrictive pericarditis. Seventeen years earlier in 1970 when the patient was 21 years old, Hodgkin's disease (stage IIIB) had developed. During 1970 and 1972, the patient received radiotherapy (6,400 rads) and chemotherapy (Mustargen [mechlorethamine hydrochloride], Oncovin [vincristine sulfate], Natulan [procarbacine hydrochloride], and prednisone), and was considered cured. In the autumn of 1986, he began to experience exertional dyspnea and swelling of the lower extremities. New York Heart Association functional status was assessed as class III-IV. Cardiac catheterization revealed constrictive pericarditis and a patent foramen ovale (see Table 1). Coronary angiography showed mild stenosis of the first obtuse marginal branch. In July and August 1987, two episodes of syncope occurred because of paroxysmal complete atrioventricular (AV) block.

Pericardiectomy for postirradiation constrictive pericarditis was performed 17 years after the initial treatment. The pericardium was exposed through a left anterolateral thoracotomy. Pleural effusions were drained (0.8 L from the left side and 1.7 L from the right side of the chest). Because of severe adhesions of the thickened pericardium, decortication had to be done by sharp dissection. The anterior and lateral pericardium was excised from the left pulmonary vein to the right phrenic nerve, with a sling of pericardium left with the left phrenic nerve. The epicardium of the anterior wall and especially the outlet of the right ventricle was densely thickened and could not be excised completely because of myocardial fibrosis. The epicardium over the right outflow tract was released by crossed incisions. A permanent pacemaker was inserted. Central venous pressure decreased from 20 mm Hg for a mean arterial pressure of 60 mm Hg before thoracotomy to 14 mm Hg for a mean arterial pressure of 70 mm Hg after thoracotomy.

The early postoperative course was uneventful. However, the clinical condition of the patient slowly deteriorated, and he died of biventricular failure 3 months after operation. Postmortem examination showed massive perivascular interstitial myocardial fibrosis, especially in the right ventricle, and endocardial fibrosis. Mild but diffuse coronary arteriosclerosis was found but without major stenoses of the main coronary arteries. Perihilar interstitial pulmonary fibrosis was also present. There was no evidence of residual Hodgkin's disease.

Comment

Pericardiectomy for postirradiation constrictive pericarditis is a procedure with a high operative mortality and poor late results. A series of 46 patients, including the 2 reported here, who underwent pericardiectomy for postirradiation constrictive pericarditis was collected from the literature (Table 2) [1–7]. Twenty-six of these patients died after pericardiectomy. The early mortality (less than 30 days) in the compiled series was 22% (10/46) and the late mortality, 35% (16/46). Only 20 patients (43%) were long-term survivors. Even if some of the cited causes of death are not directly related to the procedure (infection, progression of underlying malignancies), they appear to be typical for patients with postirradiation constrictive pericarditis, and the cumulated outcome after operation is extremely disappointing. This is in contrast to the excellent results of pericardiectomy for other reasons. In our hands, hospital mortality for the latter group is less than 3%, and the New York Heart Association functional status at control 6 months after operation is almost normal (mean class, 1.3 ± 0.4).

We believe that the poor outcome of pericardiectomy for postirradiation constrictive pericarditis is due to the coexistence of different kinds of radiation-induced damage, such as fibrosis of the myocardium and the lung, injury to other structures of the heart including the coronary arteries, the valves, and the conducting system, and the poor local (chest wall) and general condition of the patient. It has been confirmed clinically and experimentally that irradiation can cause myocardial fibrosis [8, 9], which probably is responsible for some of the poor operative results. Brosius and colleagues [8] studied 16 patients who had received more than 3,500 rads to the heart. The fibrous tissue located between myocardial cells

Table 2. Summary of Review of Literature on Pericardiectomy for Postradiation Constrictive Pericarditis

Reference	No. of Pericardiectomies	Patients With Pericarditis[a]	Average Dose (rads)	Deaths Among Patients With Pericarditis[a]	
				<30 Days	>30 Days
Seifert et al [1]	71[b]	(25)	(4,393)	(4)	8
Greenwood et al [2]		6	4,072	0	5
Cameron et al [3]	95[b]	29	4,513[c]	6	0
Coltart et al [4]		2	3,950	1	0
Stalpaert et al [5]	39	1	?	0	1
Applefeld et al [6]		5	4,490	1	1
Westerhof and Vander Putte [7]		1	7,000	1	0
Ni et al [present report]		2	7,200	1	1
Total		46	. . .	10 (22%)	16 (35%)
Average dose[d]		. . .	4,626	. . .	. . .
Early and late mortality[e]		26/46 (57%)			
Late survival		20/46 (43%)			

[a] Pericarditis means postirradiation constrictive pericarditis. [b] Data were from the same center; numbers in parentheses were not used for calculations. [c] Average dose was available for 20 of the 29 patients. [d] This was calculated for 35 patients with sufficient data in the cited reports. [e] The following causes of death were reported for the 26 nonsurvivors: heart failure, 8; infection, 4; progression of malignancy, 3; respiratory failure, 4; postradiation pulmonary fibrosis, 3; death in tabulam 1; bleeding, 1; and unknown, 4.

(interstitial myocardial fibrosis) increased in amount in half of the patients. Therefore, the increased filling pressures in patients with postirradiation constrictive pericarditis are due mainly to the increased myocardial stiffness. The pathogenesis of postirradiation myocardial fibrosis could be related to capillary endothelial cell injury, leading to a quantitative loss of capillaries, failure of the microcirculation, and ischemia [9].

It has been recommended that biopsy of the myocardium be performed before pericardiectomy for postirradiation constrictive pericarditis. The finding of extensive myocardial damage should discourage the physician from suggesting pericardiectomy because poor results have to be expected [10]. However, it is difficult to correlate the degree of sclerosis with the degree of functional loss. Postirradiation myocardial fibrosis is a gradually aggravating process. It is not secondary to pericardial constriction. After pericardiectomy, the process will continue. Myocardial fibrosis is different from myocardial atrophy, which tends to recover after pericardiectomy.

Pulmonary fibrosis is another complication of radiation therapy. It causes respiratory failure and plays an important role in mortality after pericardiectomy for postirradiation constrictive pericarditis (see Table 2). Pulmonary fibrosis was suspected in our patients before operation. The vital capacity of patient 1 was only 66% of expected and at operation, the limitation of the right lung was found. Patient 2 had only 26% of expected vital capacity. Though the decrease of vital capacity is not parallel to the degree of pulmonary fibrosis, the data are still suggestive.

Irradiation can cause mediastinal fibrosis, which destroys anatomical landmarks and results in dense adhesions [4, 11]. Epicardiectomy and pericardiectomy in this environment is technically difficult, and removal of the epicardial peel can be impossible because of the underlying myocardial fibrosis. The operation lasts longer, and blood loss is increased. The release of the heart is likely to be unsatisfactory. These problems can contribute to the high operative mortality and the difficult postoperative course.

As Brosius and associates [8] pointed out, "It is now clear that high-dose irradiation can cause damage to the epicardial coronary arteries and allow intimal proliferation of mainly fibrous tissue to produce luminal narrowing." Of their 16 young patients, 6 showed 75% cross-sectional narrowing of major epicardial coronary arteries (right, left main, left anterior descending, and left circumflex), primarily by fibrous plaques. Dunsmore and co-workers [12] reported the cases of 3 patients who sustained a myocardial infarction at an untimely age, 4 to 12 years after radiation therapy for Hodgkin's disease. Both of our patients showed some changes in the coronary arteries at angiography.

High-degree AV block after radiation therapy is uncommon, but when it happens, it is an important threat. Furthermore, it could be an expression of deep intracardiac damage. Kereiakes and associates [13] collected 7 cases of radiation-induced high-degree AV block. All patients received more than 4,000 rads to the chest. The interval to development of high-degree AV block ranged from less than 1 year to 23 years (median time, 14 years). In our patient 2, complete AV block occurred 17 years after irradiation and made his situation critical.

Damage to the endocardial wall and valves is more common. These structures are thickened by fibrous tissue. The thickening is often relatively mild and not sufficient to produce valvular dysfunction [8]. However, in some cases, it causes valvular problems of hemodynamic significance [10]. In summary, impaired cardiac function after high-dose irradiation of the mediastinum appears to be due to an impaired organ or the overall condition of the patient.

A thorough analysis of the cited reports shows that an average dose of 4,626 rads was given to 35 patients undergoing pericardiectomy for postirradiation constrictive pericarditis for whom the data were sufficient (see Table 2). The mean dose (± the standard deviation) applied to survivors was 3,904 ± 707 rads (range, 3,100 to 4,850 rads) versus 5,217 ± 1,363 rads (range, 3,540 to 8,000 rads) to nonsurvivors. The difference is significant ($p < 0.05$) and confirms that high doses applied to the heart cause severe damage. However, the reported doses suggest also that severe cardiac damage (potentially leading to death) has to be expected in patients who receive doses around 4,000 rads, not just those patients receiving excess irradiation.

In conclusion, complete epicardiectomy and pericardiectomy may not be achieved in all patients with postirradiation constrictive pericarditis. The combination of high-dose irradiation, untimely coronary artery disease, evidence of myocardial fibrosis, AV conduction disturbances, valvular dysfunction, major pulmonary fibrosis, cachexia, and recurrent mediastinal tumor should discourage a surgical approach.

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Surgical Excision of Intracardiac Myxomas: A 20-Year Follow-up

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Since November 1968, 54 patients have undergone excision of an intracardiac myxoma, which was located in the left atrium in 46 (85%), in the right atrium in 6 (11%), and in the right ventricle in 2 (4%). There were 35 female and 19 male patients with a mean age of 48 ± 14 years (range, 7 to 68 years). Four patients were asymptomatic; the others were seen mostly with exertional dyspnea, palpitation, signs of systemic illness, and syncopal episodes. Before operation, embolic episodes occurred in 13 patients with a left atrial myxoma. There were two early (3.7%) and two late deaths (3.8%). Actuarial survival at 20 years is 91% ± 4%, and most of the current survivors are asymptomatic at a mean follow-up of 6.5 ± 5 years (range, 0.2 year to 20 years). Noninvasive reevaluation was performed with echocardiographic studies in 44 patients and 24-hour electrocardiographic monitoring in 34. No instances of tumor recurrence were observed, and there was a low incidence of major supraventricular arrhythmias late postoperatively. We conclude that excision of intracardiac myxomas is curative and long-term survival is excellent. The transseptal approach provides adequate exposure and allows complete removal of the tumor regardless of its location.

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Myxomas are the most frequent benign tumors involving the cardiovascular system [1, 2]. Since 1954, when Crafoord [3] reported the first successful excision of a left atrial (LA) myxoma, myxomas have been diagnosed and removed with increasing frequency because of the widespread use of echocardiography. Nevertheless, although management of cardiac myxomas has been the subject of many recent reports [4–13], the long-term fate of the patients has been less frequently evaluated in large series. The purpose of this report is to present the early and late results, discuss some technical details, and assess by noninvasive techniques the current status of survivors by reviewing our 20-year experience with surgical intervention for intracardiac myxomas.

Material and Methods

Patient Profile

From November 1968 to December 1988, 54 patients underwent excision of an intracardiac myxoma at our institution (Table 1). There were 19 male and 35 female patients with a mean age at operation of 48 ± 14 years (range, 7 to 68 years). The tumor was located in the left atrium in 46 patients (85%), in the right atrium in 6 (11%), and in the right ventricle in 2 (4%). Mean age was 50 ± 13 years for patients with an LA myxoma and 41 ± 13 years for those with a right atrial (RA) myxoma; the 2 patients with a right ventricular (RV) myxoma were 17 and 21 years old [14].

Four patients (7%) were asymptomatic. The major preoperative symptoms in the others included exertional dyspnea in 25 (46%), palpitation in 24 (44%), and syncopal episodes in 9 (17%); low-grade fever was present in 13 patients (24%), increased erythrocyte sedimentation rate in 14 (26%), and hypochromic anemia in 5 (9%). Preoperatively, 48 patients were in sinus rhythm, and 6, all with an LA myxoma, were in chronic atrial fibrillation; episodes of paroxysmal supraventricular tachycardia were documented in 2 of them. Four patients (7%) had pleural effusions and 4 (7%), mild to moderate pericardial effusions. Embolic episodes occurred in 13 patients (24%), all of whom had an LA myxoma, and represented the first manifestation of the tumor in 10. In 1 of these 10 patients who was seen with acute lower-limb ischemia, histological examination of the embolic material disclosed the presence of myxoma cells, thereby prompting emergency excision of the tumor. Two patients, both with an LA myxoma, were seen with acute pulmonary edema, and another patient underwent successful excision of an LA myxoma during pregnancy [15]. Mitral valve incompetence was present in all patients with an LA myxoma, and was trivial to mild in 43 and moderate in 3.

The first 2 patients in this series were referred with the diagnosis of mitral valve stenosis, and the presence of an LA myxoma was an incidental intraoperative finding. In the remaining 52 patients, the diagnosis was made by cardiac catheterization and angiography in 9 (17%), by a combination of angiography and M-mode echocardiog-

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Table 1. Summary of Clinical Characteristics of Patients With Cardiac Myxoma

	Tumor Location		
Variable	Left Atrium	Right Atrium	Right Ventricle
No. of patients	46	6	2
Male/female	16/30	1/5	2/0
Age (yr)			
Mean	50 ± 13	41 ± 13	. . .
Range	7–68	27–59	17, 21
Preoperative symptoms			
Asymptomatic	3	0	1
Exertional dyspnea	20	4	1
Nocturnal dyspnea	4	0	0
Pulmonary edema	2	0	0
Palpitation	19	4	1
Chest pain	4	0	0
Low-grade fever	11	2	0
Increased ESR	10	3	1
Hypochromic anemia	3	2	0
Systemic emboli	13	0	0
Syncope	7	2	0
Pleural effusion	3	1	0
Pericardial effusion	4	0	0
Preoperative rhythm			
Sinus rhythm	40	6	2
Atrial fibrillation	6	0	0

ESR = erythrocyte sedimentation rate.

raphy in 22 (42%), and by echocardiography alone (M-mode or two-dimensional) in the last 21 (40%).

Operation was undertaken on an emergency basis in most of the patients. Associated surgical procedures were performed in 3 patients, all with an LA myxoma: double coronary artery bypass grafting in 1 patient with coronary atherosclerotic disease, mitral annuloplasty in 1 patient with myxomatous mitral regurgitation, and bioprosthetic mitral valve replacement in another patient also with myxomatous mitral regurgitation.

Surgical Technique

With the exception of the first patient in this series, who was operated on through a left thoracotomy, a median sternotomy incision was employed in all patients. Operation was performed with moderately hypothermic cardiopulmonary bypass, topical cooling, and since 1977, the adjunct of cold potassium cardioplegia. Both the superior vena cava and the inferior vena cava were routinely cannulated separately through the right atrium regardless of the position of the myxoma, with care taken to avoid any undue manipulation of the heart.

Myxomas in the left atrium were excised through the right atrium and incision of the interatrial septum (transseptal approach) in 29 patients (63%), through a combined right and left atriotomy (biatrial approach) in 10 (22%), and through a left atriotomy alone in 7 (15%); all patients with an RA or RV myxoma were operated on through a right atriotomy (Table 2). The aim of operation was to remove not only the whole mass but also its base of attachment. This goal was achieved by wide excision of the interatrial septum with patch closure of the resulting septal defect when the tumor was attached, as in most instances, to the fossa ovalis, or by excision of the surrounding endocardium and part of the underlying myocardium when the tumor was attached elsewhere. In some patients with an LA myxoma attached at other than the interatrial septum, the fossa ovalis was opened in a flaplike fashion, and after removal of the mass, it was closed by direct suture [16].

When handling the mass, great care was always taken to avoid fragmentation and therefore potential systemic embolization. At the end of the procedure, all cardiac chambers were routinely explored to rule out coexistent tumors. When a myxoma was accidentally fragmented during removal, the heart was generously irrigated with cold saline solution, and before release of the aortic cross-clamp, the aortic root or the pulmonary trunk was opened and explored to further exclude possible washout of neoplastic particles. Any associated intracardiac pathological process was dealt with concomitantly during the single aortic cross-clamp period.

Follow-up

Operative survivors were reevaluated during the interval from July to December 1988. Follow-up ranged from 0.2 year to 20 years (mean follow-up, 6.5 ± 5 years) with a cumulative duration of 351 patient-years. Three patients could not be traced; hence, follow-up was 94% complete. In most instances, follow-up was conducted by means of direct hospital visit, which included clinical evaluation, echocardiographic studies (M-mode, two-dimensional, and Doppler) to assess cardiac performance and rule out tumor recurrences, and 24-hour monitoring of the electrocardiogram, particularly in patients who had extended resection and patch reconstruction of the interatrial sep-

Table 2. Surgical Approach and Operative Findings

	Left Atrium		Right Atrium		Right Ventricle	
Variable	No.	%	No.	%	No.	%
Approach						
Transseptal	29	63	0	0	2	100
Biatrial	10	22	0	0	0	0
Left atrial	7	15	0	0	0	0
Right atrial	0	0	6	100	0	0
Location						
Fossa ovalis	26	57	4	67	0	0
Base of interatrial septum	9	20	1	17	0	0
Outflow of pulmonary veins	8	17	0	0	0	0
Left atrial roof	3	7	0	0	0	0
Suprahepatic segment of IVC	0	0	1	17	0	0
Pulmonary infundibulum	0	0	0	0	1	50
Interventricular septum	0	0	0	0	1	50

IVC = inferior vena cava.

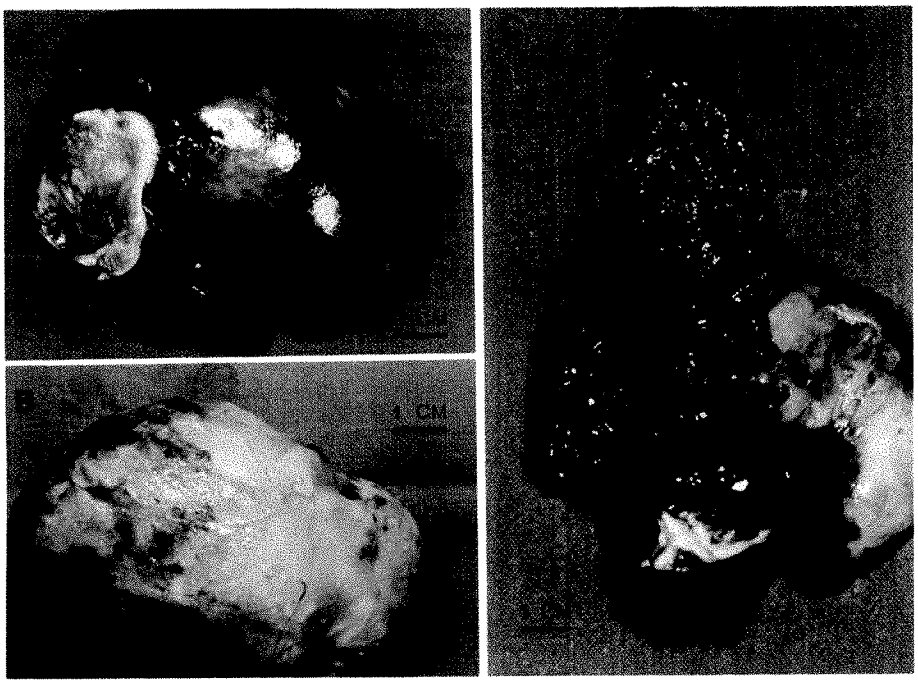

Fig 1. Gross appearance of a variety of left atrial myxomas: (A) tumor excised with a cuff of interatrial septum; (B) myxoma with a smooth surface; and (C) myxoma with a villous surface.

tum. For patients with an LA myxoma, preoperative M-mode echocardiographic data, when available, were compared using Student's t test with data obtained at follow-up. A p value of less than 0.05 was considered significant.

Results

Surgical Findings

Left atrial myxomas were attached to the fossa ovalis in 26 patients (57%), to the base of the interatrial septum close to the mitral valve annulus in 9 (20%), between the orifices of the pulmonary veins in 8 (17%), and to the LA roof in 3 (7%) (see Table 2). Right atrial myxomas were attached to the fossa ovalis in 4 patients, to the base of the interatrial septum in 1 patient, and to the suprahepatic portion of the inferior vena cava in 1. Right ventricular myxomas were located on the free wall of the pulmonary infundibulum or in the interventricular trabeculated septum.

Pathological examination of all tumors was routinely performed. Weight ranged from 5 to 89 g (mean weight, 40 ± 21 g) for LA myxomas and from 70 to 106 g (mean weight, 84 ± 19 g) for RA myxomas ($p < 0.05$); the two RV myxomas weighed 14 and 25 g. The external appearance of the tumors was usually that of a gelatinous, sessile mass with either a villous or smooth surface (Fig 1). Frequently, areas of hemorrhage were observed within the neoplasm.

Early and Late Results

There were two operative deaths (<30 days) (3.7%), both involving patients with an LA myxoma. The cause of death was intraoperative hemorrhage in 1 and bowel infarction in the other. Major early postoperative complications occurred in 11 patients: episodes of supraventricular arrhythmia, controlled with medical treatment, in 8; sternal wound dehiscence in 2; and postoperative bleeding in 1.

There were two late deaths (3.8%); 1 patient died of myocardial infarction 17 months after excision of an LA myxoma associated with aortocoronary bypass grafting, and 1 died of bowel carcinoma 5 years after operation for an RA myxoma. The patient who underwent operation during pregnancy had an uncomplicated gestation and delivered at term a healthy baby [15]. Two patients underwent successful reoperation after excision of an LA myxoma; 1 had mitral valve replacement for severe mitral regurgitation after 7 years, and the other had replacement of a failing mitral bioprosthesis after 21 months.

Actuarial survival is 91% ± 4% at 10 and 20 years (Fig 2). Of 47 current survivors surveyed, 45 are in functional class I and 2 are in class II; 42 are in sinus rhythm, and 4, all having excision of an LA myxoma, are in atrial fibrillation. The latter, 2 of whom had mitral valve replace-

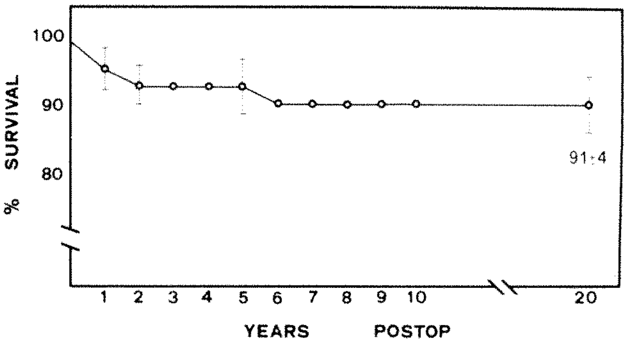

Fig 2. Actuarial survival after excision of an intracardiac myxoma.

ment, are maintained on a regimen of digoxin and diuretic agents, and 3 of the patients currently in sinus rhythm are taking antiarrhythmic drugs. Finally, 1 patient has an atrial ectopic rhythm.

Noninvasive Evaluation

Postoperative echocardiographic studies were performed in 39 patients with an LA myxoma, 4 with an RA myxoma, and 1 with an RV myxoma 0.8 year to 16 years (mean interval, 7 ± 4 years) after operation. For 20 patients with an LA myxoma, preoperative and postoperative echocardiographic data were available for comparison. The analysis showed a significant reduction of the LA diameter (47 ± 9 versus 33.6 ± 7 mm; $p < 0.001$). Left ventricular systolic (34 ± 8 versus 34 ± 6 mm; p = not significant) and diastolic (52 ± 7 versus 50 ± 6 mm; p = not significant) dimensions and left ventricular ejection fraction (68% ± 12% versus 69% ± 9%, p = not significant) were unchanged. Residual mild mitral incompetence was detected in 7 patients.

Data on 24-hour electrocardiographic monitoring were available for 34 patients postoperatively. Twenty-nine had had excision of an LA myxoma, 4 of an RA myxoma and 1 of an RV myxoma; wide resection and patch closure of the interatrial septum had been performed in 20 of them. Apart from 2 patients with chronic atrial fibrillation, major arrhythmias were detected in 4: short runs of paroxysmal supraventricular tachycardia in 3 and atrial ectopic rhythm in 1. No correlation was found between arrhythmias, size of the myxoma, and surgical technique, although most of the arrhythmias were observed in the few patients in whom a biatrial approach was used.

Comment

Results of surgical management of cardiac myxomas have been frequently reported in the past 30 years [4–13], but data on extensive follow-up of large series of such patients are limited. In an attempt to add further information concerning the results of surgical treatment and the long-term fate of patients after excision of an intracardiac myxoma, we reviewed our experience.

Both the early and late results of intervention for cardiac myxomas are gratifying. Operative mortality in this series was low and comparable with that reported by others [6, 10], and late survival, up to 20 years postoperatively, was excellent. The only two operative deaths occurred early in our experience, and both involved patients with an LA myxoma.

The presence of a cardiac myxoma, regardless of its location, represents an absolute indication for surgical excision, which should be performed without delay once the diagnosis has been made [8, 9, 13]. Such an aggressive approach is justified by the constant threat of pulmonary or systemic embolization and occlusion of the valve orifices. We noted the latter complication in a patient with an LA myxoma who died suddenly before any surgical attempt could be made [8].

There is general agreement that radical tumor excision must include a wide resection of the base of implantation, which most often is represented by the fossa ovalis; when the tumor is attached outside the interatrial septum, removal of the endocardium, at times with part of the underlying myocardium, as with an RV myxoma [14], appears to be effective. If such guidelines are followed, the surgical intervention can be considered curative, and recurrences, which have not been observed to date in our series, can be minimized.

Recurrences of myxoma at various intervals from operation have been documented [17, 18], a finding that supports the concept of a potential malignancy of cardiac myxomas. McCarthy and colleagues [11] have identified a distinctive population of patients at higher risk for tumor regrowth, that is, those with the so-called myxoma complex characterized by lentiginosis, multiple tumors, and endocrine overactivity; on the other hand, recurrences in patients with sporadic myxomas appear to be substantially uncommon. Nevertheless, because this complication is not clearly predictable, continuous postoperative follow-up of all patients by noninvasive methods is mandatory [4, 10, 11].

There is still controversy concerning the most appropriate surgical approach to achieve complete excision of intracardiac myxomas. When dealing with LA myxomas, some surgeons prefer an LA incision posterior to the interatrial groove, as also recently advocated by DiSesa and associates [13], or even a biatrial incision [19]. Like Chitwood [2], we have found the transseptal approach through a right atriotomy extremely practical and effective. In our experience, after complete myocardial relaxation, as obtained with cardioplegic arrest, wide incision of the fossa ovalis gives access to and allows inspection of all cardiac chambers. Through this route, complete and expeditious excision of the tumor is obtained, and coexistent myxomas are ruled out. Therefore, we currently favor this approach for all intracardiac myxomas, at least as the initial step.

Some technical details deserve further comment. Careful manipulation of the myxoma is recommended to avoid fragmentation and possible embolization of this fragile structure [4, 9, 10]. When fragmentation does occur, we suggest generous irrigation of the heart with cold saline solution [9] and direct inspection of the aortic root or pulmonary trunk before release of the aortic cross-clamp. This apparently excessive precaution allowed us to recognize tumor fragments that had migrated beyond the aortic valve in 2 patients with a large LA myxoma, thus preventing a potentially life-threatening postoperative embolization.

Close follow-up of patients after excision of a cardiac myxoma is recommended unanimously [4, 10, 11]. Currently, refinement of noninvasive techniques such as two-dimensional echocardiography has allowed recognition of even small intracardiac masses [20]; consequently, these methods appear the ideal tool for a periodic assessment of patients. Echocardiographic studies done in 44 of our patients have excluded any recurrence up to 16 years postoperatively; furthermore, in those with an LA myxoma, a significant reduction of the LA diameter has been documented, while both left ventricular size and function have remained unchanged. Trivial to moderate mitral regurgitation, which was present in all patients with an

LA myxoma, has been virtually eliminated after excision of the tumor, as it was most likely caused by mechanical interference of the mass with the valvular apparatus. This concurs with the opinion that mitral incompetence is reversible, unless the valve is severely damaged by the myxomatous process [9].

A high incidence of arrhythmias and conduction disturbances early and late after resection of an LA myxoma has been reported by Bateman and colleagues [21]. Although the pathophysiological substrate of these arrhythmias was unclear, they were thought to be related to a possible surgical injury to specialized tissue and conduction pathways. In our experience, no conduction disturbances have been observed and the incidence of major supraventricular arrhythmias has been substantially low. As the latter appear to be possibly related mainly to the use of a combined biatrial approach, they might be caused by more extensive incisions and excessive retraction of the heart in this situation. These results further support our current trend to use a transseptal approach for LA myxomas.

In conclusion, the extended follow-up of patients with intracardiac myxomas shows that excision of such tumors is curative and the long-term outcome excellent. Regardless of their location, cardiac myxomas should always be approached, at least initially, through the interatrial septum. This route provides adequate exposure of the mass in most instances, allows radical excision, and is associated with a low incidence of late postoperative arrhythmias.

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Bacteremia and Sternal Infection After Coronary Artery Bypass Grafting

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Sternal wound infection remains a source of substantial morbidity and mortality after coronary artery bypass grafting. We noted an association between bacteremias and sternal wound complications in these patients. A review of 835 consecutive coronary bypass patients showed a 3.2% incidence of bacteremia and a 1.9% incidence of deep and superficial sternal wound infection. The sternal wound was the most common source of bacteremia, accounting for 59% of the infections. Coagulase-negative *Staphylococcus* was responsible for one half of the sternal wound infections. Often, a positive blood culture was the first manifestation of wound infection, occurring before local signs were manifest. We recommend multiple blood cultures in postoperative coronary bypass patients with pronounced fever. If no source of infection can be identified, sternal wound aspirate may be revealing. Appropriate early wound management can then be carried out, maximizing chances for good recovery.

(Ann Thorac Surg 1990;49:454–7)

Infection and sepsis continue to contribute to the morbidity and mortality of open heart operations. Sternal wound infection remains a particularly challenging problem. It has been our clinical impression that positive blood cultures after coronary bypass grafting, though uncommon, often herald discovery of a sternal wound infection even before local signs become evident. To determine the importance of this observed relationship, we reviewed the various sources of bacteremias in a large cohort of coronary bypass patients and determined their relationship to sternal wound infection. We believe that early identification of sternal wound infection can improve its outcome and that positive blood cultures may aid in its identification.

Material and Methods

All patients undergoing coronary artery bypass grafting at our institution during a 4-year period (1985 to 1988) were checked against a list from the microbiology laboratory of open heart operation patients who had positive blood cultures during the study period. In coronary artery bypass patients with positive blood cultures, charts were reviewed for sources of infection, other positive cultures, white blood cell counts, and clinical course. If an identical organism was isolated from another site, that site was presumed to be the source of the bacteremia. Patients received oxacillin as antibiotic prophylaxis, 1 g given intravenously every six hours starting at midnight before the operation and continuing for 48 hours. Vancomycin was substituted in patients thought to be allergic to oxacillin.

Results

Between January 1, 1985, and December 31, 1988, 835 patients underwent isolated coronary artery bypass grafting at University Hospital, Syracuse, NY. Thirty-four of these patients had one or more positive blood cultures after operation. We were unable to ascertain the total number of patients who had blood cultures drawn. Seven positive cultures were presumed to be the result of contaminated specimens after thorough chart review (Table 1). Six of the 7 patients had one or more negative cultures in conjunction with the positive culture, thus increasing the likelihood of correctly identifying a contaminated specimen [1]. Clinical evidence of bloodstream infection did not develop in any patient. These patients have been eliminated from further analysis, leaving 27 patients, an incidence of bacteremia of 3.2%. There were 5 female and 22 male patients, ranging in age from 38 to 80 years (mean age, 61 years). One patient had previous bypass grafting. The conduits used were saphenous vein in all patients, left internal mammary artery in 15, and cephalic vein in 1. The first positive blood culture occurred from three to 41 days after operation (mean, nine days; median, seven days). Thirteen different organisms were isolated from the blood cultures of these patients (Table 2). We were able to identify the source of bacteremia in all patients (Table 3). Infection in the median sternotomy wound accounted for the largest identifiable group of infections (59%). This group included 12 infections involving the sternal bone and requiring major reoperation ("deep") and 4 infections superficial to the bone treated successfully with local wound care ("superficial"). These 16 patients together make up the sternal wound infection category.

The white blood cell count at the time of positive blood cultures ranged from 4.6 to 26.8 × 10^9/L (mean, 13.9 × 10^9/L; median, 14.2 × 10^9/L). Most patients were febrile at the time blood cultures were obtained. Temperatures

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Table 1. Positive Blood Cultures Presumed to be Contaminants

Patient	Organism	No. of Positive Blood Cultures	Clinical Course
AB	*Diphtheroids*	1/4	Treated for UTI (*Proteus mirabilis*)
WM	*Streptococcus*, α-hemolytic	1/6	No evidence of infection
OP	*Streptococcus*, group D enterococcus	1/1	No evidence of infection
ER	*Staphylococcus*, coagulase-negative	1/3	Treated for UTI (*Klebsiella pneumonia*)
CS	*Staphylococcus*, coagulase-negative	1/3	No evidence of infection
CZ	*Staphylococcus*, coagulase-negative	1/3	Died of cerebrovascular accident, no evidence of infection
DG	*Staphylococcus*, coagulase-negative	1/2	No evidence of infection

UTI = urinary tract infection.

ranged from 36.9° to 40.1°C (mean, 38.9°C; median, 39.1°C). Patients with bacteremia required a length of stay in an intensive care unit from two to 111 days (mean, 25 days; median, 14 days). Hospital stays were from 13 to 159 days (mean, 48 days; median, 34 days). Six patients (22.2%) died (Table 4). Only one patient (RC) died as a direct consequence of sternal infection. He suffered hemorrhage from major vessel erosion and tracheal fistula several months after flap reconstruction of the sternum.

The overall sternal wound infection rate was 1.9%; if superficial infections were eliminated, the infection rate was 1.4%. Coagulase-negative *Staphylococcus* caused 8 of the 16 sternal wound infections. Other organisms responsible for the sternal wound infections included *Proteus mirabilis* [2], *Enterobacter, Escherichia coli, Haemophilus* influenza, group D *Streptococcus*, coagulase-positive *Staphylococcus*, and *Corynebacterium* (1 patient each).

Two patients with deep sternal wound infections requiring operation showed different organisms in the sternal wound and in the blood. One was the patient described above who later died; *P mirabilis* grew in his blood at the same time that *Enterobacter aerogenes* grew in his sternal wound. The other patient had *Corynebacterium* in the blood, while *Diphtheroids* and coagulase-negative *Staphylococcus* grew from his deep sternal infection.

Table 2. Organisms Isolated From True Positive Blood Cultures

Organism	No of Patients[a]
Staphylococcus, coagulase-negative	15
Escherichia coli	4
Proteus mirabilis	3
Pseudomonas aeruginosa	3
Streptococcus group D	3
Klebsiella oxytoca	2
Bacillus	2
Candida albicans	2
Klebsiella pneumonia	1
Enterobacter aerogenes	1
Corynebacterium	1
Haemophilus influenza	1
Staphylococcus, coagulase-positive	1

[a] Total is greater than number of patients because two organisms grew in 6 patients, and three organisms grew in 2 patients.

Comment

Sternal wound infection, with its accompanying mediastinitis and persistent osteomyelitis, remains a constant concern despite the most intense prophylactic measures. Our 1.4% incidence of deep sternal wound infection in coronary bypass patients is consistent with most reports [2–4]. Because this operation is performed so commonly, it seemed appropriate to investigate the incidence and importance of bacteremias in this group in view of its observed relationship to sternal infection.

Lockey and associates [5] reported a 2.7% incidence of bacteremia in 1,640 patients undergoing open heart operation between 1964 and 1970. Less than one fourth of these were due to endocarditis, and 14 of the 44 bacteremias were associated with sternal wound infections. Ferrazi and co-workers [6] found a 0.8% incidence of septicemia in 3,275 patients undergoing a wide variety of cardiac operations. Dandalides and co-workers [7] reported a 3.5% incidence of bacteremia in 223 patients undergoing cardiac operation in 1981 [7]. The 3.2% incidence of bacteremia in our series is similar to that noted in a large group of valve replacement patients (3.6%) previously reported from our institution [8].

A source for the bacteremia was identified in 100% of our coronary bypass patients, but in only 68.8% of the earlier valve replacement group. The mortality rate was similar in the two groups: 22.2% in the coronary bypass group and 28.1% in the valve replacement group. The

Table 3. Source of Bacteremia

Source	No. of Patients
Sternal wound	16
Line sepsis	6
Vein harvest site	1
Urine	1
Intraabdominal	1
Pleural fluid	1
Pulmonary	1

Table 4. Deaths in Patients in Whom Bacteremia Developed After Coronary Artery Bypass Grafting

Patient	Age (yr)	Sex	Organism	Source	Cause of Death
GB	66	M	*Staphylococcus*, coagulase-negative	Intraabdominal	Pancreatic abscess with intestinal infarction
JC	66	M	*Staphylococcus*, coagulase-negative	Pleural fluid	Cerebrovascular accident
GL	80	M	*Klebsiella oxytoca*	Line	Pneumonia with sepsis, cholecystitis
FM	70	F	*Klebsiella pneumonia*	Line	Low cardiac output, hepatic necrosis
RC	69	M	*Proteus mirabilis; Staphylococcus*, coagulase-negative	Sternum	Tracheal fistula, hemorrhage
EM	55	M	*Candida albicans*	Line	Pancreatitis; multiple enterocutaneous fistulas

sources of the bacteremias were quite different. In the valve replacement series were 2 patients with cases of endocarditis originating in the urinary tract, and both patients died as a result. There were no sternal wound infections in the valve replacement group. Among the coronary bypass patients, there were no cases of endocarditis, but 16 cases of sternal wound infection. *Staphylococcus epidermidis* accounted for 55% of the positive blood cultures in the coronary bypass group compared with 25% in the valve replacement group.

Clinically significant postoperative fevers should be investigated with blood cultures. Concern about endocarditis in coronary artery bypass patients is much less than in patients who have undergone valve replacement. Our results support this differential level of concern. The present review shows that bacteremia in a patient who has undergone coronary artery bypass grafting can be ominous. Coagulase-negative *S epidermidis* is the most frequent offender, and the sternal wound, the most common source. In fact, a patient who exhibits bacteremia after coronary artery bypass grafting has a 59% chance of harboring a sternal wound infection. In many such patients in our series, fever and a positive blood culture were the first manifestations of the sternal infection; local signs did not become evident until later.

The serious nature of postoperative infection, as evidenced by our mortality rate and length of hospital stay, is supported in the literature. Damen [9] found a significant relationship ($p < 0.001$) between septicemia and mortality in a group of 48 coronary bypass patients remaining in intensive care longer than 96 hours. We believe that constant vigilance can facilitate early discovery, allowing early treatment and improved outcome for patients with these infections. We obtain at least two sets of blood cultures on all postoperative cardiac surgical patients who exhibit a fever greater than 38.5°C.

Careful physical examination, including a search for local wound signs and symptoms, is carried out concurrently. If blood cultures are positive and no obvious source has been identified, a careful aspiration of the sternal wound in at least two sites after strict disinfection of the skin is performed. A small amount of saline solution, previously placed in the syringe, is used to transfer the contents of the needle to a culture tube. In this fashion, cultures can be obtained even when no obvious fluid is aspirated. We have been surprised on several occasions to find gross pus or fluid in a wound that appears to be healing normally.

If a Gram stain of the sternal aspirate confirms infection, our policy has been to immediately address the wound surgically. Several successful methods have been reported in the literature; if the bone appears strong and viable, our preference has been to open, debride, and close the sternum over continual irrigation catheters [10, 11]. However, if the sternum itself is fragmented or obviously nonviable, we prefer early wide sternal resection and rectus abdominus myocutaneous flap closure [12]. This has resulted in good clinical course and early hospital discharge in several patients. Intravenous antibiotic administration for 6 weeks is a vital part of the treatment. We have administered these at home using a Hickman catheter with good results. Owing to the high incidence of coagulase-negative *Staphylococcus* in these infections, we have recently changed our standard prophylactic antibiotic for open heart operation from oxacillin to vancomycin.

In summary, a positive blood culture in patients who have undergone coronary artery bypass grafting should prompt a careful evaluation of the sternal wound. Early treatment should result in a much improved long-term result.

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Notice From the Southern Thoracic Surgical Association

The Thirty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at the Hyatt Regency Cerromar Beach, Puerto Rico, November 8–10, 1990. There will be a $155 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 8, 1990. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1990, to Donald C. Watson, Jr, MD, Program Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic Surgery*. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1990 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1990, and forwarded to Lenox Baker, Jr, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601.

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Recent Experience With Major Sternal Wound Complications

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During a recent 1-year period, 31 patients sustained a major sternal wound infection and sternal dehiscence developed in 6 patients. Multiple potential risk factors were tabulated in these patients and in a control group selected from 1,521 patients undergoing sternotomy during the same time period. The overall infection rate was 2.1%, and the mortality rate in the patients with sternal infection or dehiscence was 16.2%. Chronic obstructive pulmonary disease, prolonged intensive care unit stay, respiratory failure, connective tissue disease, and male sex were significantly higher in the group with sternal infection or dehiscence ($p < 0.05$). Advanced age and low cardiac output episodes were more frequent in this group, but only approached statistical significance. Although several risk factors may have been interrelated, male sex and the presence of pulmonary disease were statistically independent predictors of sternal wound infection. Risk factors may be helpful in identifying high-risk patients for additional prophylactic measures.

(Ann Thorac Surg 1990;49:458–62)

Patients who undergo median sternotomy continue to suffer morbidity and death from sternal wound complications. Major complications are divided practically into two groups: sternal dehiscence alone and major sternal or mediastinal infection with or without associated sternal dehiscence. The incidence for these groups is 0.7% to 1.5%, with an associated mortality rate in adults of 13% to 33% [1, 2]. Many risk factors for these complications have been proposed; however, risk factors between institutions have differed and occasionally conflicted. Those past differences as well as potential recent effects from trends in patient selection, antibiotic prophylaxis, and technology led to the present study.

Material and Methods

Thirty-seven consecutive patients sustained major sternal wound complications during the 1988 calendar year. A major complication was defined as a median sternotomy wound infection or dehiscence severe enough to warrant reoperation. Six of these patients had sternal dehiscence without infection, and the remainder had major wound infections. Data were collected retrospectively and concurrently during the study period. These data included demographic information, factors that may affect wound healing, surgeon, assistants, and other frequent attributes of this group of patients.

Most patients had coronary artery bypass. Thirty-two had coronary artery bypass alone, 3 had valve replacement and concomitant coronary artery bypass, and 2 had valve replacement as their sole procedure. The 6 patients who had sternal dehiscence alone had coronary artery bypass as their primary procedure.

In 87% of the 31 patients with major infections, the cause was *Staphylococcus aureus* or *Staphylococcus epidermidis*. Four of these infected patients were diagnosed initially as having primary sternal dehiscence until *S epidermidis* grew in the culture obtained from the wound during sternal rewiring. Six of the staphylococcal infections were methicillin resistant.

The average interval between the original operation and the operation to treat the complication was 18 days. Most of the reoperations consisted of sternal debridement, rewiring, and continuous irrigation in a manner described by Grossi and co-workers [3]. Four patients required open wound packing with later closure of the wound using pectoralis myocutaneous flaps. Of the survivors, 1 failed to be cured by these methods and required a second rewiring for dehiscence. The 6 patients with dehiscence alone responded uneventfully to rewiring.

The number of patients undergoing median sternotomy during the same time period was 1,521, including 1,236 who had coronary artery bypass and 42 who had miscellaneous procedures. The rest of the patients underwent valvular replacement operations with or without coronary artery bypass (234 patients). The control group consisted of patients who underwent every tenth operation during the same period. These operations consisted of elective, semielective, and emergent procedures in ratios similar to those of the group with complications. The factors identified in the group with complications were then tabulated from the control group.

Antibiotics were administered intravenously on call to the operating room as routine prophylaxis. These consisted of cefazolin for the first 3 months of the year and

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Table 1. Comparison of Complication and Control Groups

Variable	Complications Group	Control Group	1988 Overall
Primary procedure	37	157	1,521
Coronary artery bypass	32	122	1,236
Valve replacement	3	18	176
Combined coronary artery bypass valve	2	13	67
Right internal mammary artery	1	0	14
Other	0	4	42
Average age (yr)	66.5	63.4	. . .
Preoperative stay (days)	6.0	5.1	. . .
Intensive care unit stay (days)	5.6	3.8	. . .
Cardiopulmonary bypass time (min)	95.4	95.4	. . .
Sex			
M (%)	81.1	63.7	. . .
F (%)	18.9	36.3	. . .
Mortality (%)	16.2	5.7	. . .

Breakdown of primary procedure, sex, mortality and several continuous variables for complicated and control groups. Of these data, only sex and mortality were statistically significant ($p < 0.05$). Age and intensive care unit stay approached significance ($p < 0.10$).

cefamandol for the remainder of the year. Irregularities in prophylactic antibiotic administration were tabulated in both groups.

Primary wound closure was performed with No. 5 parasternal steel wire; the remainder of the wound was closed in layers using absorbable suture. Bacitracin antibiotic irrigation was used liberally during each closure.

Mortality was defined as in-hospital deaths during the same or subsequent admission. Complications were grouped according to the month of the original operation. Statistical analysis for the continuous variables was performed using Student's t test; χ^2 analysis was performed for categorical data. Multiple logistic regression was used to determine risk factors independently predictive of sternal wound infection.

Results

Table 1 compares the primary procedure, mortality, and other statistics among the overall group, group with complications, and control group. The incidence of infection among patients undergoing coronary artery bypass was 2.1%, the same rate as that of patients undergoing valvular replacement. None of the patients with wound dehiscence alone died, but the mortality rate for major wound infection was 19.7%. One of the patients died of continuing sepsis, and the others died of multiorgan failure after the infection had been controlled. Morbidity among the survivors led to an average of 30 days of hospitalization beyond that required for a routine postoperative course.

The mortality rate and the incidence of male sex in the patients with complications were significantly higher than those of the control group ($p < 0.05$). Age ($p = 0.07$) and intensive care unit stay ($p = 0.10$) appeared to approach statistical significance. The rest of the continuous variables did not differ significantly.

Table 2 shows the percentage of each associated risk factor for both the control group and the group with complications. Of all the tabulated factors, only intensive care unit stay longer than three days, chronic obstructive pulmonary disease, respiratory failure, presence of connective tissue disease, or postoperative pneumonia were significantly different between the two groups. Perioperative low cardiac output was the most common finding overall, and the need for inotropic support was greater in the group with complications but did not achieve statistical significance ($p = 0.20$). Postoperative arrhythmia was usually atrial fibrillation, which occurred in 77.4% of valve patients as compared with 43.4% of coronary bypass patients. Internal mammary artery graft usage approached 60% in patients undergoing only coronary artery bypass; otherwise, the remaining risk factors had similar rates among the different operations.

The average number of the five significant risk factors was 1.11 per patient for the group with complications and 0.52 for the control group. Of the patients with complications, the average was 1.10 for those with infection and 1.17 for those with dehiscence. Multiple logistic regression showed that the presence of chronic obstructive pulmonary disease and male sex were independent predictors of sternal wound complications. The remaining risk factors did not lend much additional predictive power.

Although there was some variation in the way antibiotics were administered, the differences were not significant. About 94% of the patients in both groups received antibiotics soon enough before skin incision. There was no clear trend in the complication rates for the individual members of the operating team.

Figure 1 shows the number of patients with major sternal infections for each 2-month period of the study along with several other major variables. The plots are parallel except for July through August, when there was only one major infection.

Comment

Dehiscence-only and infection groups were combined in this study because of the possibility of common etiological factors. Early postoperative sternal instability may lead to skin separation, ingress of bacteria, and subsequent wound infection. In addition, similar clinical presentations can occasionally make differentiation difficult. Four of these patients were believed to have had dehiscence alone until the operative cultures grew organisms.

The incidence of infection among the total group is somewhat higher than that in other recent large series [1]. The reason for this is probably multifactorial. The average age of both study and control groups is higher than that of patients in previously published series. The average age of patients in these earlier reports ranged from 48.9 to 57.8 years, at least 6 to 9 years younger than our population [1, 3–6]. Some researchers [1, 3, 5, 6] have reported slightly higher average ages in their patients with complications, and the difference in this study appears to approach significance. Although age per se may not be a statistically significant risk factor, the diseases that are significant do tend to progress with age. The average age at this institution has increased partly because younger patients with less complex coronary artery disease are being treated with percutaneous transluminal coronary angioplasty. Consequently, patients with more advanced coronary disease undergo operation. This trend is occurring elsewhere, as documented in a report by King and Talley [7] in which recent data from Emory University Hospital and the National Heart, Lung, and Blood Institute registry showed a 4-year increase in average age, as well as an 11% increase in patients with low ejection fractions (<50%).

Methicillin-resistant *Staphylococcus* has become more prevalent at this institution and accounted for 22% of the mediastinal infections. Patients colonized with this organism preoperatively would have had no protection from the prophylactic antibiotics used. A small percentage of patients from both groups did not receive antibiotics before skin incision; this usually occurred in emergency situations. In any case, these data do not indicate an advantage of one prophylactic regimen over another.

A preoperative hospital stay longer than two days occurred commonly in both groups. Cruse and Fuord [8] showed that this doubled the wound infection rate for clean wounds in a large epidemiological study. Many patients with this factor were admitted with an acute problem that required time for evaluation or supportive care. Others were admitted for evaluation and were found to be at too high a risk to be discharged before operation. In either situation, patients with more complications had a longer preoperative exposure to hospital flora.

The sex of the patient has been implicated as being a risk factor for wound dehiscence and infection. One prospective study showed female sex to be a significant risk factor in wound complications whereas other reports show male predominance or no significant differences between sexes [1, 6, 9]. This study showed male sex to be significantly more frequent in the study group. The disparity in age may be related to the differences between populations of patients and the association of sex with other risk factors in those groups.

A low flow state was identified in 72.9% of patients in this series. This is somewhat higher than in previously reported series. Four of these patients (10.8%) had a metabolic acidosis in the perioperative period. Some of the acidoses were transient and many had no identifiable source. These patients were presumed to have had an episode of inadequate peripheral tissue perfusion despite a borderline acceptable cardiac index. Other investigators have implicated the "low cardiac output syndrome" as a significant factor in the development of major wound infection [3, 10]. The data in this study might have demonstrated significance if each group had more patients. The criteria were also designed to yield a high sensitivity in identifying patients with an episode of hypoperfusion. A criterion such as the need for multiple inotropic agents for a protracted period would have

Table 2. Comparison of Risk Factors

Risk Factor	Complications Group (%, n = 37)	Control Group (%, n = 157)	p Value
Perioperative low cardiac index (<2.2 L/min/m^2)	72.9	64.9	NS
Inotropes required	62.1	50.9	NS
Metabolic acidosis (pH < 7.30 requiring $NaHCO_3$ therapy)	35.1	28.0	NS
Intraaortic balloon counterpulsation	10.8	12.7	NS
Postoperative arrhythmia (atrial fibrillation or ventricular ectopy requiring treatment)	56.7	51.0	NS
Intensive care unit stay longer than 3 days (range, 2 to 35 days)	51.3	33.8	<0.05
Preoperative hospital stay longer than 2 days (range, 1 to 25 days)	51.3	51.0	NS
Left internal mammary artery as conduit	45.9	46.5	NS
Chronic obstructive pulmonary disease	43.2	14.6	<0.001
Cardiopulmonary bypass longer than 99 minutes (range, 48 to 158 minutes)	40.5	41.4	NS
Age greater than 69 years (range, 49 to 84 years)	32.4	27.4	NS
Diabetes mellitus	32.4	23.6	NS
Preoperative antibiotics not administered in usual fashion[a]	27.0	14.7	NS
Respiratory failure requiring tracheostomy	13.5	2.6	<0.01
Perioperative steroid administration for pulmonary or connective tissue disease	13.5	13.4	NS
Obesity	10.8	14.6	NS
Perioperative renal insufficiency	10.8	8.3	NS
Connective tissue disease	8.1	0.6	<0.01
Redo median sternotomy	5.4	8.3	NS
Emergency reexploration for bleeding or hemodynamics	5.4	5.1	NS
Postoperative pneumonia	5.4	0.6	<0.05
Tracheostomy preceding complication	2.7	. . .	. . .
Right internal mammary used as conduit	2.7	0.8[b]	NS

[a] Breakdown of antibiotic irregularities for complications and control groups, respectively: Antibiotics administered on call (usual): 75.7% and 85.4%; antibiotics administered in operating room: Keflin, 16.2% and 7.0%; Mandol, 2.7% and 1.9%; antibiotic not administered in time: 5.4% and 5.9%. [b] N = 1,521.

NS = not significant ($p > 0.05$).

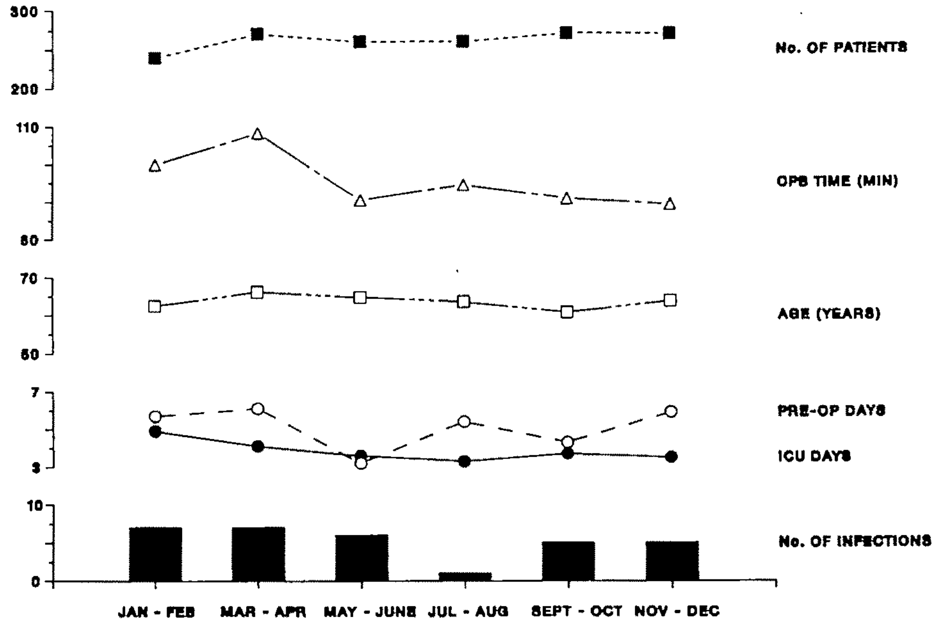

Fig 1. The number of infections for each 2-month interval remained rather constant except for July and August. The number of patients undergoing operation and other variables for the control group did not show much variation throughout the year. (CPB = *cardiopulmonary bypass;* ICU = *intensive care unit.)*

higher specificity and might be a more powerful predictor of wound complications.

The incidence of chronic obstructive pulmonary disease, respiratory insufficiency, and prolonged intensive care unit stay for ventilatory support is similar to that of previous reports [2, 3, 6]. In the series of Grossi and associates [3], the incidence of respiratory failure was 41.6%, with about 20% of the patients requiring tracheostomy about five days after the original operation. In the present series, the incidence of respiratory problems is similar except that only 13.5% required tracheostomy and only 1 patient underwent tracheostomy before the sternal complication developed. Generally, tracheostomy was performed after a longer interval (about ten days) when tissue planes from neck to the mediastinum were more likely to be obliterated. Although standard tracheostomy was performed, cricothyroidotomy may be a better choice in the postoperative setting [11].

Although postoperative pneumonia was not a frequent risk factor in the complicated group, it was statistically significant owing to its very low incidence in the control group. Other investigators have implicated postoperative pulmonary infections, as well as infections in other body regions, as substantial risk factors [3].

Certain types of cardiac operations have been associated with increased rates of wound infection. A recent collective review demonstrated no significant difference in the infection rate for valvular versus coronary artery operations [2]. Use of the internal mammary artery has been associated with increased risk of wound complications, particularly when both internal mammary arteries are used [10]. Technique and instrumentation for this operation have improved steadily, and more recent data do not show a higher complication rate [8]. When complications do occur, however, flap closure is more likely to be necessary because of the devascularization from the internal mammary artery harvest [12]. This study does not show a significant difference between the two groups for single internal mammary artery grafts, and right internal mammary artery grafts were used too infrequently to ascertain significance.

Prolonged cardiopulmonary bypass (longer than 180 minutes), which has been cited previously [10] as a risk factor, did not occur in the complication group in the present study. This difference may have resulted from improved techniques in myocardial protection because most patients required minimal postischemic cardiopulmonary bypass time for cardiac recovery. Prolonged bypass times were not required even in patients with severely depressed myocardium because of the options in mechanical ventricular assistance available today. Advanced age and diabetes were slightly more frequent in the group with complications than in the control group but the difference was not statistically significant.

Steroid administration, connective tissue disease, renal failure, and hypothyroidism were identified in several patients, but only connective tissue disease was significantly more evident in the group with complications. Technical considerations such as obesity, redo sternotomy, or emergency sternotomy were not significant risk factors in this study [13].

Only 5.4% of the patients in the group with complications had to undergo mediastinal reexploration for bleeding or hemodynamic support. This compares favorably with an 18% to 42% reexploration rate reported in other series [2]. Generally, a conservative approach to reexploration was followed provided that there was evidence of coagulopathy and hemodynamic stability. This has decreased the number of patients who would have undergone reexploration based solely on the amount of their mediastinal drainage.

Populations of patients may have different ratios of sex or other risk factors. This may account for disparities in what is published by different institutions. All of the significant factors (except for connective tissue disease) may be associated with underlying pulmonary pathology (eg, chronic obstructive pulmonary disease may be more common in a male population in which smoking is more prevalent). In this study, a significant number of the male patients with chronic obstructive pulmonary disease also had secondary diagnoses of pneumoconiosis from the prevalence of coal mining in the region. Yet these associations do not explain why male sex was a statistically independent risk factor. This may mean that there were unknown factors relating male sex to sternal wound complications.

The decrease in the infection rate for the single 2-month period in this study cannot be explained easily. Only a slight decrease in the average intensive care unit stay was noted. This time marked the beginning of the academic year when personnel turnover occurs; however, no member of the operating team was associated with a high infection rate. Variables such as patient selection and the degree of resident involvement during this time period are difficult to measure.

Although the infection rate in this study is somewhat higher than those of earlier studies, the mortality rate for major complications compares favorably [2]. As in the series of Grossi and co-workers [3] (28% mortality) only 1 of the deaths resulted from ongoing sepsis, with the remainder of the deaths caused by multiorgan failure. With use of closed drainage, most patients can be managed with a single reoperative procedure.

Multiple factors contribute to major sternal complications. These data support respiratory and connective tissue diseases as being significant risk factors. Postoperative low cardiac output may be a major contributory factor to sternal complications, but this study did not show statistical significance. Other items such as the patient's sex can vary in significance probably because of differences in the populations studied. In this report, male sex and the presence of chronic obstructive pulmonary disease were both independent predictors for sternal wound complications. Certain surgical considerations such as the type of open heart procedure or type of coronary conduit no longer appear to be important predictors.

An increase in the complication rate may be occurring because of inadequate prophylactic antibiotic coverage and the increasing age and disease severity in patients referred for operation. Using factors to identify high-risk patients for additional interventions may be an approach to diminish the incidence of these complications.

We thank James D. Schlosser for assistance in statistical analysis of the data.

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Appendix 1. Technique of Sternal Closure

Once we achieved adequate hemostasis we placed drainage tubes and irrigated each wound with 250 mL of saline solution containing 50,000 U of bacitracin. Six No. 5 stainless-steel wires were used to reapproximate the sternum. Two wires were placed in the manubrium, and the remainder were placed parasternally. Thin or fractured sternal edges were approximated by looping the wire behind each opposing costosternal articulation to create a mattress closure. The sternal edges were approximated, and the wires were twisted and cut. The sternal fascia was closed with running 1-0 polyglycolic suture, and interrupted nonabsorbable suture was used to approximate the upper abdominal fascia. 2-0 absorbable suture was used to close the subcutaneous space, and a subcuticular skin closure was performed using 3-0 Dexon suture.

Prostaglandin E_1 and Intrapulmonary Shunt in Cardiac Surgical Patients With Pulmonary Hypertension

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Unlike many other vasodilators, prostaglandin E_1 may reduce pulmonary vascular resistance without changing intrapulmonary shunt in patients with adult respiratory distress syndrome. Whether the same is true for surgical patients with cardiogenic pulmonary hypertension but normal gas exchange remains unclear. Data from the intraoperative records of 8 patients with pulmonary hypertension and elevated pulmonary vascular resistance were used for the study. Hemodynamic variables had been monitored through radial arterial cannulas and pulmonary arterial catheters. Arterial and mixed venous oxygen tension, carbon dioxide tension, oxygen saturation, and hemoglobin level, as well as cardiac output and pulmonary capillary wedge pressure, had been determined in each patient before prostaglandin E_1 infusion was started and again when the desired pulmonary vascular response had been achieved. Pulmonary and systemic vascular resistances and intrapulmonary shunt were calculated from standard formulas. Infusion rates of prostaglandin E_1 ranged from 7 to 135 ng/kg/min. Prostaglandin E_1 reduced mean pulmonary arterial pressure, pulmonary vascular resistance, and pulmonary capillary wedge pressure but did not change intrapulmonary shunt. Heart rate and mean arterial and right atrial pressures were not changed, whereas systemic vascular resistance decreased and cardiac output increased. The present study shows that prostaglandin E_1 reduces pulmonary arterial pressure and pulmonary vascular resistance without dramatic changes in intrapulmonary shunt in patients with pulmonary hypertension secondary to cardiac disease.

(Ann Thorac Surg 1990;49:463–5)

Prostaglandin E_1 (PGE_1) is a monoenoic eicosinoid produced endogenously in small quantities by cyclooxygenation of dihomo-γ-linolenic acid. The compound has antiinflammatory, antiplatelet, and vasodilating effects and has been used extensively to maintain patency of the ductus arteriosus in pediatric patients with ductus-dependent congenital heart disease [1]. In adults, PGE_1 has been used in the treatment of pulmonary hypertension due to a variety of causes [2], left ventricular failure secondary to acute myocardial infarction [1], peripheral vascular disease [3], Raynaud's disease [4], and adult respiratory distress syndrome [5]. Data have also been published that demonstrate the efficacy of PGE_1 in reducing right ventricular afterload and in improving pump function after mitral valve replacement or cardiac transplantation [6, 7].

Although animal models indicate an inhibition of hypoxic vasoconstriction and an apparent increase in intrapulmonary shunt fraction (Q_S/Q_T) [8, 9] during PGE_1 infusion, this does not appear to be true in normal humans [10]. Additional data suggest that PGE_1 does not alter oxygenation or Q_S/Q_T in patients with pulmonary hypertension and impaired gas exchange [5], although more recent investigation has provided conflicting results [11]. It has been our clinical impression that PGE_1 used intraoperatively to treat pulmonary hypertension does not alter arterial oxygen tension, suggestive of well-maintained ventilation/perfusion relationships. In contrast, other vasodilators, such as sodium nitroprusside, produce a decrease in arterial oxygen tension presumably by inhibiting hypoxic vasoconstriction and increasing Q_S/Q_T [12].

The present study was performed as a retrospective analysis to document the influence of PGE_1 on arterial oxygenation and calculated Q_S/Q_T in patients with cardiogenic pulmonary hypertension but relatively normal gas exchange.

Method and Materials

Data from the anesthetic records of 8 patients with pulmonary hypertension and elevated pulmonary vascular resistance were used for the study after permission had been granted by the Human Studies Committee of our institution. Four patients had undergone cardiac transplantation, 3 had undergone mitral valve replacement (2 for stenosis, 1 for insufficiency), and 1 had undergone removal of biventricular assist devices. In 3 patients (1 with mitral insufficiency, 2 for transplantation), PGE_1 infusion had been started after sternotomy but before institution of cardiopulmonary bypass; in the other 5 patients PGE_1 was started after weaning from cardiopulmonary bypass or ventricular assist devices.

Hemodynamic variables were monitored through radial arterial cannulas and pulmonary arterial catheters capable

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Table 1. Individual Patient Data, Prostaglandin E_1 Dose and Time-Course of Administration, Changes in Systemic and Pulmonary Arterial Pressures, and Changes in Intrapulmonary Shunt

Procedure	PGE_1 Dose (ng/kg/min)	Pre/Post CPB	Δ in MAP (mm Hg)	Δ in MPAP (mm Hg)	Q_S/Q_T
Transplantation	40	Pre	3	27	−0.9
Transplantation	20	Pre	16	19	+1.6
Transplantation	30	Post	8	6	+9.5
Transplantation	50	Post	13	15	−4.5
MVR for MS	7	Post	4	7	+0.4
MVR for MS	10	Post	16	13	−6.5
MVR for MR	135	Pre	2	12	+5.8
Removal of Bivad	30	Post	5	8	+2.7

Bivad = biventricular assist device; CPB = cardiopulmonary bypass; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; MR = mitral regurgitation; MS = mitral stenosis; MVR = mitral valve replacement; PGE_1 = prostaglandin E_1; Q_S/Q_T = intrapulmonary shunt.

of measuring mixed venous oxygen saturation. Patients were anesthetized with lorazepam and fentanyl or sufentanil and paralyzed with vecuronium, and their lungs were ventilated with 100% oxygen. Other agents administered included volatile anesthetics, nitroglycerine, dobutamine, and isoproterenol; all had been instituted before PGE_1 infusion and were not altered during the period of time considered.

Arterial and mixed venous oxygen tension, carbon dioxide tension, oxygen saturation, and hemoglobin level (1306 pH/blood gas analyzer and 482 co-oximeter, Instrumentation Laboratories), as well as thermodilution cardiac output and pulmonary capillary wedge pressure, had been determined for each patient before PGE_1 infusion was started (through the pulmonary artery catheter introducer) and again when the desired pulmonary vascular responses to PGE_1 had been achieved.

Pulmonary and systemic vascular resistances were calculated from standard formulas. Intrapulmonary shunt was calculated as:

$$Q_S/Q_T = CcO_2 - CaO_2/CcO_2 - CvO_2,$$

where: CcO_2 = oxygen content of pulmonary capillary blood

$$(Hb \times 1.39)S_AO_2 + (P_AO_2 \times 0.0031),$$

CaO_2 = oxygen content of arterial blood

$$(Hb \times 1.39)S_AO_2 + (P_AO_2 \times 0.003), \text{ and}$$

CvO_2 = oxygen content of venous blood

$$(Hb \times 1.39)SvO_2 + (PvO_2 \times 0.003);$$

PaO_2 = arterial oxygen tension, PvO_2 = venous oxygen tension, S_AO_2 = oxygen saturation of pulmonary capillary blood, and P_AO_2 = oxygen tension of pulmonary capillary blood (from alveolar gas equation).

Changes produced by PGE_1 infusion were analyzed by *t* test; *p* values less than 0.05 were regarded as significant.

Results

Surgical procedure, time-course of PGE_1 infusion, maximum PGE_1 dose, changes in systemic and pulmonary arterial pressures, and changes in Q_S/Q_T are shown in Table 1. Maximum doses for the 2 patients who underwent mitral valve replacement for stenosis were 7 and 10 ng/kg/min, respectively; systemic hypotension was the limiting factor. Doses ranged from 40 to 135 ng/kg/min in the other patients. In all patients, dose rates were titrated to their final level within 10 minutes of initiation of the infusion. There was no apparent correlation between dose and change in Q_S/Q_T.

Hemodynamic and intrapulmonary shunt data obtained before and during PGE_1 infusion are shown in Table 2. Mean pulmonary arterial pressure, pulmonary vascular resistance, and pulmonary capillary wedge pressure all decreased, whereas Q_S/Q_T did not change. Heart rate, mean arterial pressure, and right atrial pressure were not changed by PGE_1 infusion, whereas systemic vascular resistance decreased and cardiac output increased. Prostaglandin E_1 infusion was continued in the postoperative period in all patients except the 1 who underwent mitral valve replacement for regurgitation. Despite the antiplatelet action of PGE_1, none of the patients required reexploration for postoperative bleeding.

Table 2. Influence of Prostaglandin E_1 on Hemodynamics and Intrapulmonary Shunt[a]

Variable	Baseline	PGE_1
MPAP (mm Hg)	41 ± 3	27 ± 3[b]
PCWP (mm Hg)	22 ± 3	15 ± 2[b]
MAP (mm Hg)	72 ± 4	66 ± 4
RAP (mm Hg)	12 ± 1	10 ± 1
CO (L/min)	4.8 ± 0.4	6.1 ± 0.6[b]
HR (beats/min)	92 ± 9	94 ± 9
PVR (dynes-s/cm^5)	343 ± 38	190 ± 44[b]
SVR (dynes-s/cm^5)	1077 ± 95	803 ± 119[b]
Q_S/Q_T (%)	10.7 ± 0.3	12.1 ± 1.7

[a] Data are mean ± standard error of the mean. [b] $p < 0.05$

CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PGE_1 = prostaglandin E_1; PVR = pulmonary vascular resistance; Q_S/Q_T = intrapulmonary shunt; RAP = right artery pressure; SVR = systemic vascular resistance.

Comment

Our data demonstrate that PGE$_1$ decreases mean pulmonary arterial pressure and pulmonary vascular resistance without dramatically altering Q_S/Q_T in anesthetized, ventilated patients with pulmonary hypertension secondary to cardiac disease. The data also suggest that reduced pulmonary arterial pressure and vascular resistance may result in part from a decrease in left atrial pressure and increased cardiac output.

Previous investigation indicated that PGE$_1$ reduces pulmonary arterial pressure and vascular resistance without altering Q_S/Q_T in patients with adult respiratory distress syndrome [5]. More recent data, however, have provided conflicting results [11]. In addition, other studies in a sheep model of noncardiogenic pulmonary hypertension demonstrate an increase in Q_S/Q_T during PGE$_1$ infusion [13, 14]. In the present study, pulmonary hypertension was primarily the result of cardiac disease; baseline gas exchange was relatively normal and Q_S/Q_T before PGE$_1$ infusion ranged between 10% and 13%, values not unusual for anesthetized, ventilated patients. Thus, care must be taken in comparing results from the present study with those from previous studies in which pulmonary hypertension resulted from an inherently pulmonary cause.

The mechanism by which PGE$_1$ may maintain intrapulmonary blood flow distribution despite marked reduction in pulmonary arterial pressure and vascular resistance remains enigmatic in light of animal data indicating that the drug inhibits hypoxic vasoconstriction [9]. Potential reasons for the disparity include species variation, enormous differences in dose, the etiology of pulmonary hypertension, and nonpulsatile lung perfusion models.

Prostaglandin E$_1$ is a relatively selective pulmonary vasodilator because 80% to 90% of the drug is cleared during passage through the pulmonary circulation. At high infusion rates more drug reaches the systemic circulation to cause peripheral vasodilatation. In the present study, PGE$_1$ doses were relatively low in comparison with those used in animal investigation; the limiting factor was systemic hypotension. In many of our patients, a degree of systemic vasodilatation was undoubtedly beneficial and contributed to reduced left ventricular end-diastolic pressures and increased cardiac output.

Of particular interest was the finding that dose-limiting reductions in systemic arterial pressure developed in our 2 patients with long-standing mitral stenotic disease at relatively low infusion rates of PGE$_1$. Our findings are consistent with a previous report by D'Ambra and colleagues [6] showing that left atrial infusion of norepinephrine was required to maintain systemic blood pressure during PGE$_1$ infusion for right ventricular dysfunction after mitral valve replacement. Because structural changes of the pulmonary vascular endothelium produced by long-standing pulmonary hypertension may diminish extraction of PGE$_1$ during circulation through the lungs, the drug should be used judiciously in patients with this condition.

When larger patient populations with higher PGE$_1$ doses are considered, significant increases in intrapulmonary shunt may become apparent. We recently observed, however, that equipotent pulmonary vasodilating doses of PGE$_1$ and sodium nitroprusside in the same patient produced 5% and 45% increases in Q_S/Q_T, respectively [15]. Thus, although PGE$_1$ may be expected to increase intrapulmonary shunt slightly, the response may be less prominent than with other vasodilators such as nitroprusside. We conclude that PGE$_1$ represents a valuable perioperative adjunct to optimize cardiac function, while maintaining oxygenation, in patients with limited cardiopulmonary reserve.

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Surgical Cure of Automatic Atrial Tachycardia by Partial Left Atrial Isolation

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Partial left atrial isolation was performed in a 16-year-old girl with persistent atrial tachycardia refractory to antiarrhythmic agents for 3 years. Intraoperative atrial epicardial and endocardial mapping showed that the earliest atrial activation occurred in an area lateral to the junction of the right superior pulmonary vein and the left atrium. An incision isolating the right half of the left atrial body containing the area of the earliest atrial activation and both right pulmonary veins from the remainder of the left atrium was made. The incision was then reapproximated. An excision encircling the interatrial septum containing the upper anterior portion of the septum with early activation was also made, and the atrial septal defect was repaired with a pericardial patch. The patient has been in sinus rhythm and free of arrhythmia for a follow-up period of 12 months.

(Ann Thorac Surg 1990;49:466–8)

Surgical excision or cryoablation of the arrhythmia focus has been successfully achieved in a few patients with automatic atrial tachycardia [1–5]. This arrhythmia has been less amenable to surgical therapy because it is less predictable and cannot be induced electrically with programmed stimulatory techniques. In this communication, we report on a patient with refractory automatic atrial tachycardia whose arrhythmia was cured by partial isolation of the left atrium.

A 16-year-old girl was admitted to the hospital for consideration of surgical management of incessant supraventricular tachycardia. Routine laboratory determinations including thyroid studies and chest roentgenogram were within normal limits. Electrocardiograms showed atrial tachycardia with variable atrioventricular block and with a ventricular rate of 160 to 220 beats per minute; propranolol (20 mg every 6 hours), nadolol (80 mg/day), quinidine sulfate (300 mg every 6 hours), procainamide (500 mg every hour), disopyramide (100 mg every 6 hours), and amiodarone (200 mg every 12 hours), alone or in combinations, had been prescribed sequentially but had failed to control the arrhythmia. The result of cardiac catheterization was normal.

The electrophysiological study was performed in the postabsorptive, nonsedated state. Mapping of atrial activation sequence showed that the site of the earliest atrial activation was in the anterior atrial septal area. Rapid atrial pacing suggested that the tachycardia was automatic in nature.

A median sternotomy was performed. A reference electrode was sewn to the right atrial appendage. Epicardial mapping was done before cannulation. During this period, fortunately, the rhythm was that of atrial tachycardia, with rates of 140 to 200 beats per minute. Recording over both atria identified the site of the earliest atrial activation to be located at an area lateral to the junction of the right superior pulmonary vein and the left atrial body (Figs 1A, 2A).

Under normothermic partial cardiopulmonary bypass, atrial septal mapping was done through the right atriotomy, and the site of the earliest septal activation was located anterior to the fossa ovalis (Fig 2B).

Under ischemic cardioplegic cardiac arrest, the portion of the left atrium containing the confluence of the right pulmonary veins was then isolated from the remainder of left atrium (Fig 2A). The isolated left atrium, along with the attached right pulmonary veins, was then reapproximated with a single running suture.

An encircling excision of the interatrial septum containing the early activation area over the superior limbus and portion of the fossa ovalis was also performed. The created atrial septal defect was then repaired with a bovine pericardial patch (Fig 2B).

Electrocardiographic recording obtained after the cardiopulmonary bypass showed a sinus rhythm. Mapping of the atrial tachycardia focus revealed a spontaneously firing electrical activity at a rate of 214 beats per minute; however, this site now was dissociated from the remainder of the heart (Fig 1B).

The postoperative course was uneventful. Twelve-lead electrocardiograms as well as a 24-hour ambulatory electrocardiographic monitoring study performed before discharge revealed a normal sinus rhythm. The patient has remained in sinus rhythm without arrhythmias for a follow-up period of 12 months.

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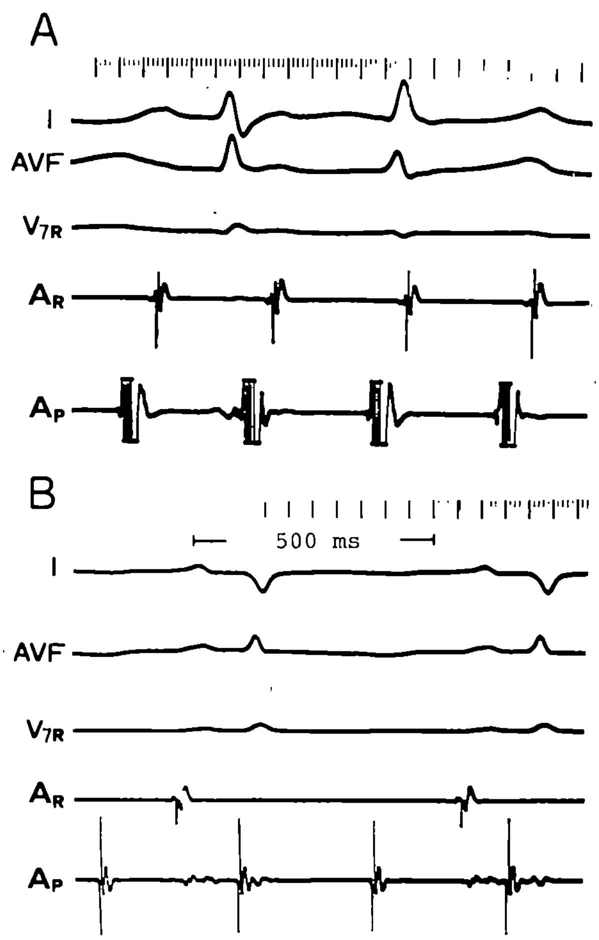

Fig 1. Epicardial atrial mapping before and after partial atrial isolation. Atrial electrograms were recorded from reference electrodes located at the right atrial appendage (A_R) and the probe electrodes (A_P). The probe electrodes were located at an area lateral to the junction of the right superior pulmonary vein and the left atrium in both panels. Recording before atrial isolation (A) showed atrial tachycardia at a cycle length of 255 ms. The atrial electrogram recorded from the probe electrodes was registered 70 ms earlier than that recorded from atrial reference. Recording after atrial isolation (B) showed dissociation of electrical activities between the probe electrodes and the reference electrodes. (V_{7R} = ventricular reference lead.)

Comment

Atrial tachycardias can be seen as paroxysmal attacks, repetitive salvos, or even persistent and continuous racings. Paroxysmal atrial tachycardias have been attributed to either reentry or automaticity. The atrial tachycardia in our patient is consistent with the latter category.

Several new therapeutic methods have been developed to treat refractory automatic atrial tachycardia. His bundle interruption using catheter electrocoagulation, operative cryoablation, or surgical incision, accompanied by permanent ventricular pacing or coupled atrial pacing, is effective in controlling the ventricular rate [6]. Nonetheless, it renders patients pacemaker dependent. Coumel and colleagues [1] obtained transient success using electrocoagulation. Wyndham and co-workers [2] successfully excised the tachycardia focus from the right atrial appendage. Subsequently, using epicardial or endocardial cryoablation or focal atrial excision, alone or in combination, Ott and associates [4] and Seals and colleagues [5] have been successful in treating a limited number of children and adults, respectively. Transvenous catheter ablation has been successfully described in children with automatic atrial tachycardia located in the right atrium [7].

The concept of atrial isolation was introduced by Cox and co-workers [8]. They described the technique of left atrial isolation in 1980 and subsequently developed the technique of right atrial isolation in dogs [9]. Anderson and asssociates [10] performed an encircling excision that excluded the portion of left atrium containing the focus of atrial tachycardia and both the right pulmonary veins in a 37-year-old man. The technique used in this report is identical to that of Anderson and associates. Normal atrioventricular conduction and hemodynamics are preserved with this technique. In our patient, however, the encircling excision of the interatrial septum may not have been necessary. We were uncertain that the arrhythmia did not arise from the septum during operation.

In conclusion, we believe that partial atrial isolation is an effective approach in select patients with troublesome automatic atrial tachycardia.

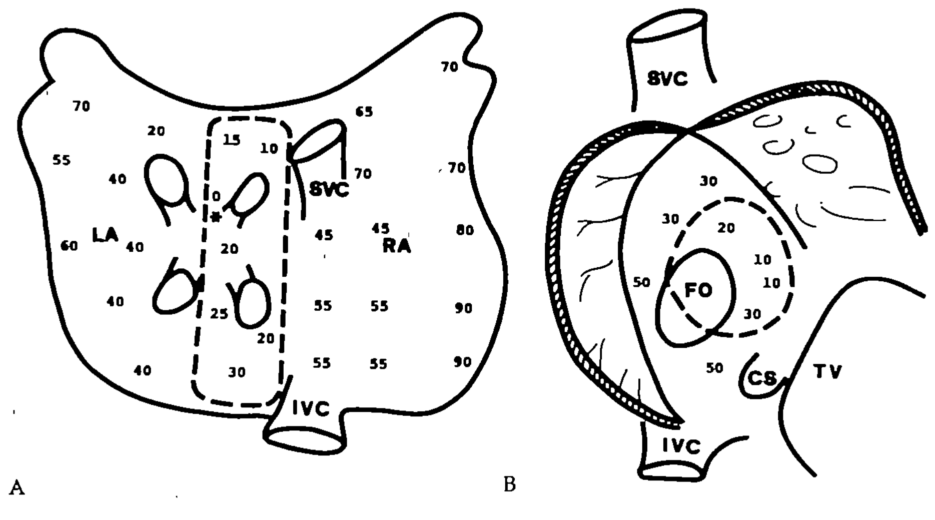

Fig 2. Atrial activation time obtained from atrial mapping during atrial tachycardia and before partial atrial isolation. (A) Mapping from the atrial epicardial surface. (B) Mapping of interatrial septum obtained from the right atrial cavity. The earliest atrial activation was registered from the area lateral to the confluence of the right superior pulmonary vein to the left atrium (as indicated by an asterisk). (CS = coronary sinus; FO = fossa ovalis; IVC = inferior vena cava; LA = left atrium; RA = right atrium; SVC = superior vena cava; TV = tricuspid valve. Dashed lines represent incision lines.)

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Dissection of the Left Main Coronary Artery: Diagnosis by Angioscopy

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A 58-year-old woman with mitral valve disease was investigated with cardiac catheterization. At catheterization, a suspected dissection of the left main coronary artery occurred. This diagnosis was confirmed at urgent operation by intraoperative angioscopy. The patient underwent mitral valve replacement and coronary artery bypass grafting and made a good postoperative recovery. Coronary angioscopy at operation provides a useful means of diagnosing pathology in the left main coronary artery.

(Ann Thorac Surg 1990;49:469–70)

Left main coronary artery dissection is a rare and serious complication of coronary angiography [1]. Confirmation of the dissection by further angiography carries the risk of extending the lesion. We describe a case of a 58-year-old woman in whom coronary dissection occurred as she was being investigated for mitral valve disease. The diagnosis was subsequently made at operation by angioscopy.

A 58-year-old woman with known mitral valve disease was admitted for investigation of increasing shortness of breath on exertion. She underwent cardiac catheterization, which revealed a tight mitral stenosis with good left ventricular function. Selective coronary angiography was performed, and the left coronary artery was easily engaged with a size 4 left Judkins catheter. The first injection opacified the left coronary artery, but screening to set up for cineangiography showed a small quantity of contrast medium lingering in the region of the left main coronary artery (Fig 1). This cleared within one minute. A sinus flush of the left coronary artery showed contrast medium that appeared to have extravasated out of the left main coronary artery. No further views were taken because of the risk of the dissection extending if a further coronary injection was made. The patient remained pain-free and hemodynamically stable throughout the procedure.

In view of these findings, the patient was taken to urgent operation. The heart was cannulated for cardiopulmonary bypass. After cross-clamping of the aorta, cold crystalloid cardioplegic solution was infused into the aortic root. During this infusion, a 2.4-mm diameter angioscope (Olympus PF246, Keymed, Essex, United Kingdom) was inserted into the aortic root through a small stab wound and secured with a pursestring suture on a "snugger." The angioscope has no angulation system; however, it was possible to manipulate the scope by advancing it through the aortotomy and by simultaneously rotating it between finger and thumb. In this way, the aortic valve and both coronary ostia were easily visualized. The aortic root and aortic valve appeared normal; however, there was a dissection seen at the origin of the left main coronary artery (Figs 2–5) with thrombus lying in the lumen of the vessel.

In view of the risk of thrombotic obstruction of the left main coronary artery, bypass grafting to the left anterior descending coronary artery was performed using the left internal mammary artery. The coronary artery was 1.5 mm in diameter and healthy at this site. The circumflex coronary artery was nondominant with small obtuse marginal branches and was not grafted. The mitral valve was replaced using a 31-mm St. Jude valve. The heart came off bypass without difficulty and the postoperative course was uneventful. The patient was discharged on the seventh day postoperatively, and at follow-up 2 months later she was well.

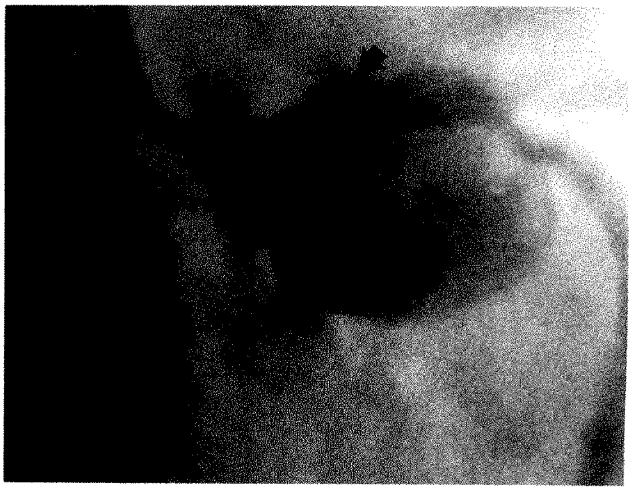

Fig 1. Right anterior oblique view of a left sinus flush angiogram depicting contrast medium lying outside the left main coronary lumen (arrow).

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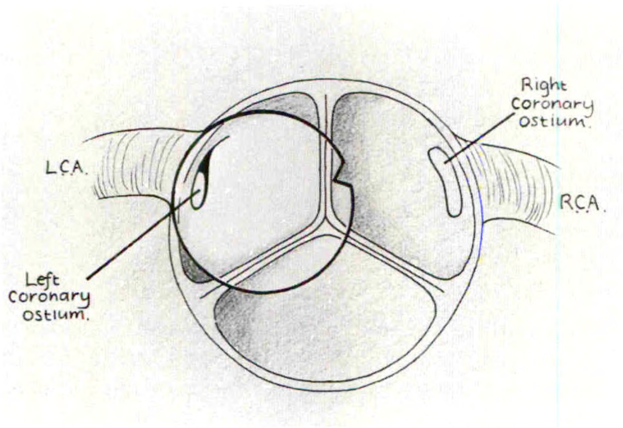

Fig 2. Transverse section of the aortic root at the level of the aortic valve. The area shown in Figure 3 is highlighted. (L.C.A. = *left coronary artery;* R.C.A. = *right coronary artery.)*

Comment

Angioscopy is not a new technique. A rigid angioscope was first developed in 1913 [2]. The constant beating of the heart and the opacity of blood were major obstacles in these early attempts. Recently, the limitations of angiography and the increase in intravascular interventional procedures have led to a renewed interest in the subject [3].

Modern-day cardiopulmonary bypass with crystalloid cardioplegic arrest provides an ideal setting for coronary angioscopy, and this is made possible with the development of ultrathin flexible fiberoptic endoscopes. The use of these instruments to delineate intravascular detail at operation has been described [4]. Coronary angioscopy has been used to confirm angiographic findings and to assess anastomoses during bypass grafting. In this case, angioscopy confirmed the diagnosis and indicated the need for coronary artery grafting in addition to mitral valve replacement.

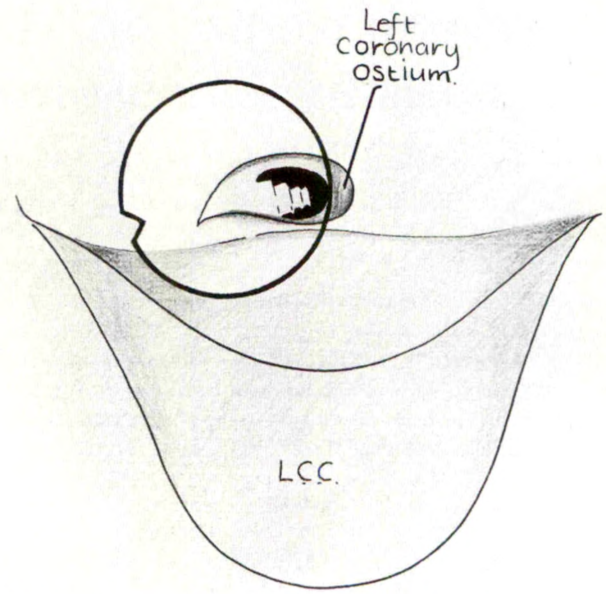

Fig 4. Appearance of the ostium of the left main coronary artery positioned above the left coronary cusp of the aortic valve. The area shown in Figure 5 is highlighted. (L.C.C. = *left coronary cusp.)*

We acknowledge David Crawford for drawing the illustrations and Isobel Bush for preparing the manuscript.

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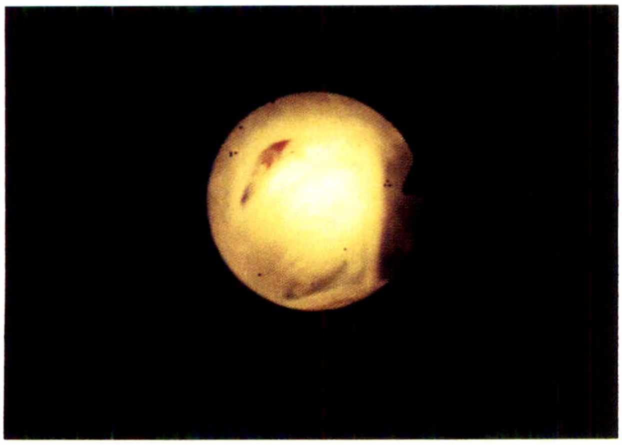

Fig 3. Angioscopic photograph of the left coronary cusp of the aortic valve. The ostium of the left main coronary artery can be seen with thrombus at the site of the dissection.

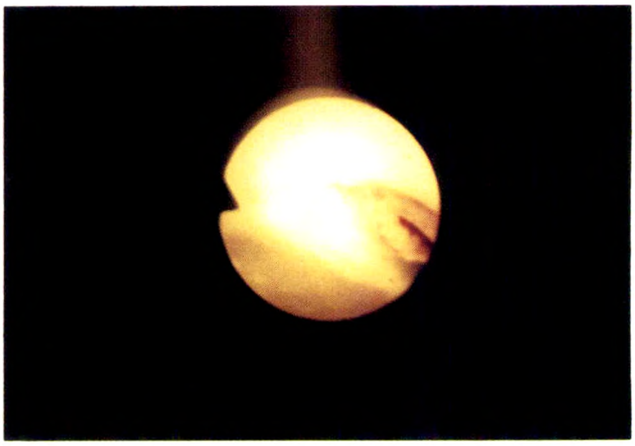

Fig 5. Angioscopic photograph of the ostium of the left main coronary artery. Part of the intimal tear can be seen. There is fresh thrombus within the lumen.

Early Manifestation of Noncalcific Aortic Stenosis After Porcine Valve Replacement

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Symptoms of noncalcific aortic stenosis developed in a 57-year-old man 3 months after implantation of a Carpentier-Edwards porcine heterograft. The glutaraldehyde-processed bioprosthesis was removed 7 months after implantation and replaced with a No. 3 Medtronic Hall valve.

(Ann Thorac Surg 1990;49:471–2)

Calcific stenosis in bioprostheses has been documented in children [1, 2] and in patients on dialysis with severe renal failure [3, 4]. We report a 57-year-old man in whom noncalcific aortic stenosis developed 3 months after porcine aortic valve replacement.

The patient had exercise intolerance and dyspnea on exertion. He had had a heart murmur, diabetes, and hypertension for years. He had a normal venous pressure, a large left ventricle, and a harsh grade 4/6 systolic murmur with a short diastolic murmur at the second left sternal border. There was a 70-mm Hg gradient across the aortic valve with a valve area of 0.58 cm^2 and 4+ aortic valve calcification. Pulmonary artery pressure was 28/12 mm Hg (mean, 17 mm Hg) and a left ventricular end-diastolic pressure was 14 mm Hg. The patient had 1+ aortic insufficiency, normal coronary arteries, and global left ventricular hypokinesis with an ejection fraction of 28%.

In May 1987, the patient underwent operation for aortic valve replacement with a 25-mm Carpentier-Edwards porcine valve prepared according to specifications by American Edwards (Santa Ana, CA). Cardioplegia was performed using a 4°C blood base solution having 20 mEq of potassium per liter and a cooling jacket. Aortic cross-clamp and bypass times were 111 and 172 minutes, respectively.

The postoperative period was uncomplicated. On the ninth postoperative day, the patient was placed on a regimen of Coumadin (crystalline warfarin sodium). He underwent in-hospital cardiac rehabilitation and was discharged on a regimen of 10 mg of Coumadin daily. At the time of discharge, no cardiac murmur was heard.

Follow-up

The patient improved clinically until 2 months after discharge, when progressively increasing dyspnea on exertion began. The patient had a grade 3/6 systolic murmur at the left sternal border, a normal venous pressure, and a blood pressure of 180/100 mm Hg. Three months later, the patient had paroxysmal nocturnal dyspnea and increased dyspnea on exertion. His venous pressure was 10 cm H_2O, and he had a grade 4/6 systolic murmur at the left sternal border with transmission to both carotid arteries; a systolic thrill was palpated at the second right intercostal space with a biventricular heave. The electrocardiogram showed left ventricular hypertrophy without evidence of a new myocardial infarction. The chest roentgenogram showed cardiac enlargement with some congestion. An echo-Doppler study indicated a 64-mm Hg gradient across the aortic valve. Cardiac catheterization showed a mean right atrial pressure of 9 mm Hg, a pulmonary artery pressure of 65/30 mm Hg (mean, 30 mm Hg), a mean wedge pressure of 28 mm Hg, a left ventricular systolic pressure of 230 mm Hg, a left ventricular end-diastolic pressure of 32 mm Hg, and a coronary artery pressure of 155/80 mm Hg (mean, 110 mm Hg). The peak aortic gradient was 85 mm Hg, and the average valve area was 0.64 cm^2. Cardiac output was 4.25 L/min. The left ventricular angiogram showed diffuse hypokinesis with 1+ mitral insufficiency. Coronary angiogram showed no changes. During follow-up, the patient remained on Coumadin therapy. His prothrombin time ranged from 21 to 23 minutes with normal control of 12 seconds.

At operation, the ring of the valve was not visible. The leaflets were intact and noncalcified, but were equally covered with a heavy layer of a white, dense material that prevented the valve from opening completely. The central opening was 3 mm. There was no evidence of fresh or old thrombi. The valve was removed, the annulus was incised, and a No. 3 Medtronic Hall valve was inserted.

Pathology

The ventricular surface of the valve was macroscopically normal. The cusps were easily separated. With forceps, the center of the valve could be opened 3 mm (Fig 1). The arterial side was covered with an easily removable white material 3 mm thick. This material was tightly packed close to the valvular ring and less compact toward the center (Fig 2). There were no lesions in the cusps, and the commissures were not fused.

Histologically, the valvular cusps were intact and lined with endothelium. A thick granular fibrin plug filled the

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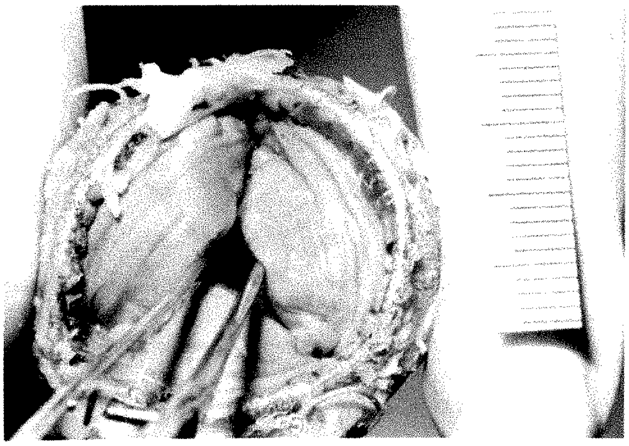

Fig 1. Demonstration of orifice in Carpentier-Edwards porcine aortic valve at time of removal (7 months after initial placement).

arterial side of the valve. No evidence of inflammatory infiltrates, microorganisms, or calcification was noted. A diagnosis of fibrin plaques was made by surgical pathology.

Comment

Early calcific stenosis in adults appears to occur less frequently than in children or in patients with severe renal failure. Early noncalcific stenosis due to fibrin deposition on porcine valvular cusps has not been reported.

On valves removed 1 to 2 months after implantation, investigators have observed layers of fibrin, especially on outflow surfaces. The accumulated change in fiber deposition is visible only microscopically [5, 6].

Our case report is of particular interest in that fibrin deposits large enough (3 mm thick) to cause symptoms indicative of clinically significant aortic stenosis occurred after valve implantation. This case shows that fibrin deposition on valve surfaces can begin soon after implantation and can be thick enough to cause clinically significant stenosis. Initially, progression of the patient's symptomatology was attributed to left ventricular dysfunction.

Attention to patients' symptomatology and physical findings should alert physicians to the possibility of early aortic stenosis. Furthermore, absence of radiographic or echocardiographic evidence of calcium deposition on valve leaflets should not preclude the diagnosis of aortic stenosis in the early follow-up period.

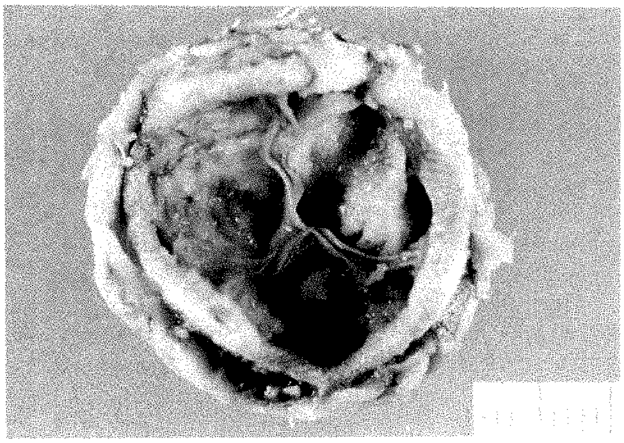

Fig 2. Arterial surface of Carpentier-Edwards porcine aortic valve after removal of deposits that covered each valve leaflet.

We thank Mira J. Betts for secretarial support in manuscript preparation.

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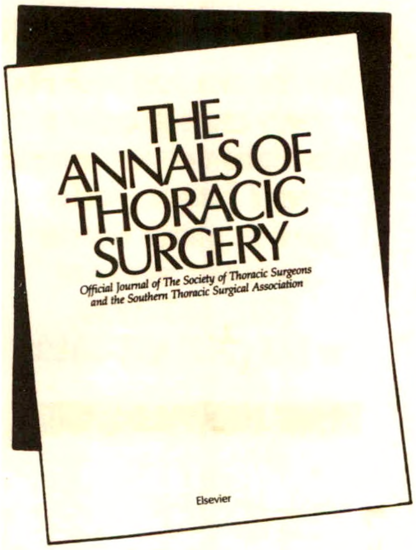
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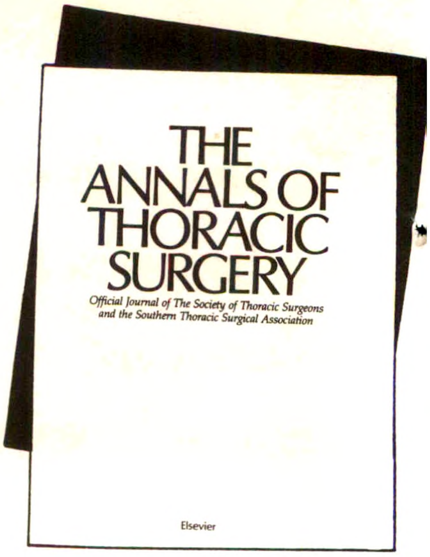
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Cor Triatriatum, Coarctation of the Aorta, and Ventricular Septal Defect: A Rare, Surgically Correctable Anomaly

Masahiro Yamaguchi, MD, Yasuyuki Nishikawa, MD, Yuhei Hosokawa, MD,
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A case of cor triatriatum associated with coarctation of the aorta and ventricular septal defect, successfully treated surgically by a staged approach, is reported. This combination is a very uncommon but potentially correctable cause of congestive heart failure and death in infancy. Early accurate diagnosis aided by an awareness of this combination and prompt surgical correction should yield excellent long-term results.

(Ann Thorac Surg 1990;49:473–5)

Cor triatriatum is a rare congenital cardiac anomaly characterized by an abnormal partitioning of the left atrium by a fibromuscular membrane that divides the left atrium into a proximal or "accessory" and a distal or "true" chamber. In most cases, the proximal chamber receives all the pulmonary veins and the distal chamber contains the atrial appendage and empties into the left ventricle through the mitral valve. Associated cardiovascular anomalies occur commonly in patients with this malformation [1–4].

We report a case of cor triatriatum associated with coarctation of the aorta (CoA) and ventricular septal defect (VSD) successfully treated surgically in infancy. This combination appears to be quite exceptional in clinical reports.

The patient was admitted with mild cyanosis, tachypnea, and failure to thrive at age 4 months. Physical examination on admission showed a poorly nourished male infant weighing 3,854 g with a grade 2/6 systolic murmur best heard in the third intercostal space at the left sternal border and a blood pressure difference of 26 mm Hg between the upper and lower extremity. Chest roentgenogram showed cardiac enlargement (cardiothoracic ratio, 0.61) and increased pulmonary vasculature. Electrocardiogram showed severe right ventricular hypertrophy. Two-dimensional echocardiogram showed a VSD of moderate size, an atrial septal defect (ASD), and a patent ductus arteriosus. Counter-current aortography through a radial artery disclosed a severe preductal CoA (Fig 1).

The patient underwent surgical repair of CoA on an emergency basis. Through a posterolateral thoracotomy in the third intercostal space, the patent ductus arteriosus (4 mm) was doubly ligated and a segment of preductal coarctation was enlarged from 4 to 7 mm by subclavian flap aortoplasty. Postoperatively, the blood pressure difference disappeared completely.

The patient had an uneventful postoperative recovery and was discharged from the hospital in satisfactory condition. His later postoperative course was complicated, however, with persistence of tachypnea and slow weight gain, and he underwent cardiac reevaluation at age 1 year 2 months (body weight, 4,900 g). Repeated echocardiography revealed an abnormal membrane subdividing the left atrium into a proximal (accessory) chamber that communicated with the right atrium through the ASD and a distal (true) chamber that contained the mitral valve (Fig 2).

Cardiac catheterization data are shown in Table 1. There was a step-up of oxygen saturation at the right atrium with a pulmonary to systemic flow ratio of 3.3. Pulmonary artery pressure was elevated to equal to systemic pressure. Pulmonary arterial wedge pressure was also elevated to a mean of 19 mm Hg, and a mean pressure gradient of 5 mm Hg was noted between the accessory and true chamber. The left ventriculogram demonstrated a VSD of moderate size and satisfactory postoperative status of CoA. Pulmonary arteriogram showed a shunt through the ASD but failed to identify an abnormal membrane in the left atrium.

The patient was operated on with the diagnosis of cor triatriatum, VSD, and ASD. With use of cardiopulmonary bypass and moderate hypothermia, the right atrium was opened. Inspection of the left atrium through the ASD (12 mm) disclosed an abnormal diaphragm with an opening of 10 mm. This membrane subdivided the left atrium into an accessory chamber that received all the pulmonary veins and communicated with the right atrium through the ASD and a true chamber that contained the left atrial appendage and mitral valve. There was no communication between the true chamber and the right atrium. Complete excision of the intraatrial membrane and patch closure of the ASD and VSD (10 mm) of perimembranous inlet type were performed using aortic cross-clamping, cold blood cardioplegia, and topical cooling. The VSD was exposed through the tricuspid valve.

The postoperative course was uneventful. At cardiac catheterization 1 month after operation, the patient's

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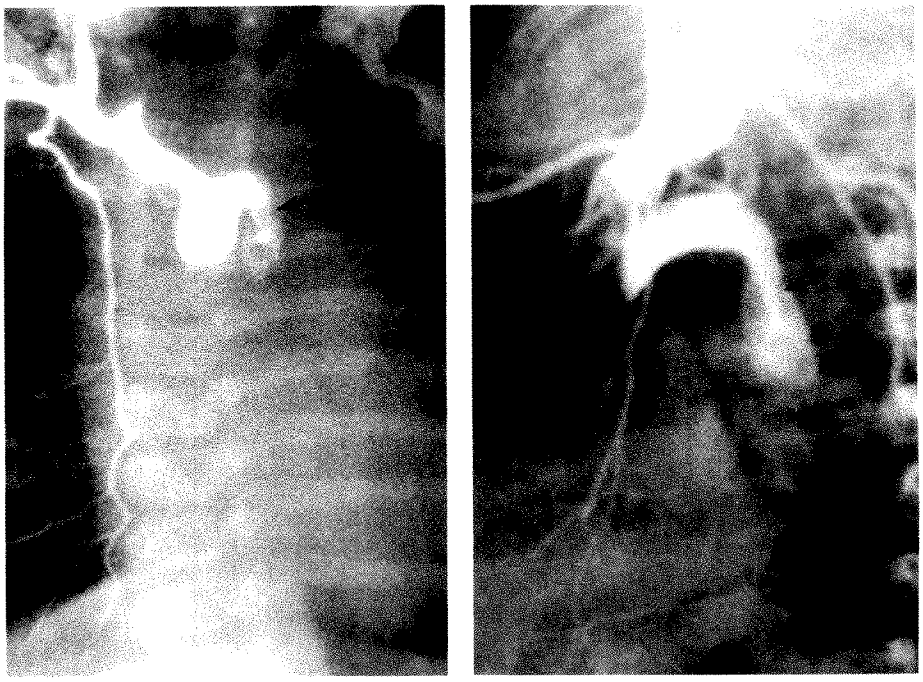

Fig 1. Counter-current aortogram through the right radial artery, frontal view (left) and lateral view (right). Black arrow *shows the site of coarctation.*

pulmonary arterial pressure decreased markedly and there was no left-to-right shunt. Two years after operation, he was doing well and his echocardiogram was considered normal.

Comment

Cor triatriatum is a rare congenital anomaly occurring in only 0.4% of all congenital cardiac anomalies [5]. In this anomaly, the proximal and distal chamber communicate through a stenotic fenestration in the membrane, which manifests symptoms and signs of pulmonary venous obstruction. It may have clinical features that mimic anomalous pulmonary venous drainage or mitral stenosis depending on the presence or absence and the location of a defect in the atrial septum.

Table 1. Cardiac Catheterization Data

	Oxygen	
Location	Saturation (%)	Pressure (mm Hg)[a]
Superior vena cava	65	14/5 (10)
Inferior vena cava	69	12/3 (8)
Right atrium	84	13/1 (8)
Right ventricle	87	81/0 (38)
Pulmonary artery		
Trunk	89	79/29 (53)
Left	89	77/27 (50)
Pulmonary artery wedge (left)	89	23/10 (19)
Pulmonary vein (left)	99	22/8 (15)
True chamber of left atrium	99	15/7 (10)
Left ventricle	99	83/0 (38)
Brachial artery	. . .	80/46 (57)

[a] Mean pressure is shown in parentheses.

The reported incidence of associated anomalies in patients with cor triatriatum vary from 24% to 80% in clinical and postmortem series [1–4]. Common associated anomalies are patent ductus arteriosus, anomalous pulmonary venous drainage, persistent left superior vena cava, VSD, tetralogy of Fallot, atrioventricular canal, and double-outlet right ventricle. Association of severe CoA appears to be very rare and was reported in only 2 cases among 16 autopsy cases by Marin-Garcia and associates [2]. Previously, diagnosis of cor triatriatum has been common at postmortem examination or at the time of operation for correction of associated lesions [1, 2]. More recently, preoperative diagnosis has been aided by a better awareness of the anomaly and advances in M-mode and two-dimensional echocardiographic diagnosis and cardiac catheterization procedures [3, 4, 6, 7]. When the lesion is associated with other cardiac anomalies, however, accurate preoperative diagnosis is more difficult because hemodynamic alterations and clinical findings vary according to the type and severity of associated defects, sometimes masking the presence of the triatrial heart.

Two-dimensional echocardiography at our patient's admission failed to disclose the abnormal left atrial membrane and the symptoms caused by the CoA masked the presence of the triatrial heart. The persistence of tachypnea and slow weight gain under medical control, unusual in an infant after CoA repair with a VSD of moderate size, caused us to reevaluate this patient. Retrospectively, we should have repeated echocardiography earlier in this patient after considering his clinical course. Recent improvement in the surgical results of symptomatic infants and neonates with CoA is largely attributable to noninvasive early diagnosis and operation. In infants with CoA and VSD, it has been our policy to repair the CoA within 24 hours of diagnosis and repair VSD electively as a second-stage operation [8]. Had the initial diagnosis been

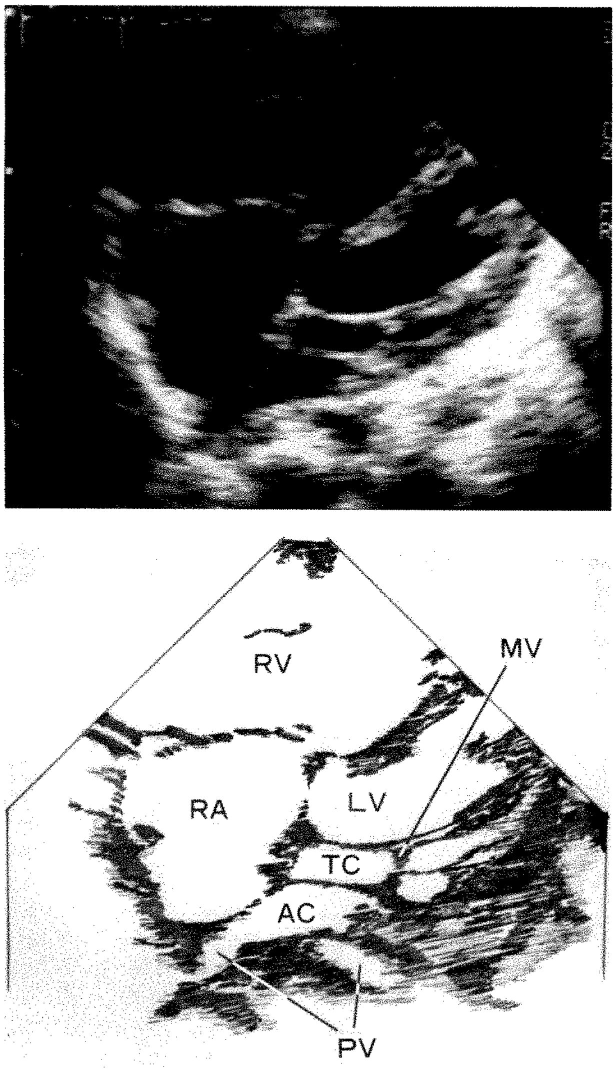

Fig 2. Two-dimensional echocardiogram (four-chamber view). (AC = *accessory chamber;* LV = *left ventricle;* MV = *mitral valve;* PV = *pulmonary vein;* RA = *right atrium;* RV = *right ventricle;* TC = *true chamber.)*

correct, we would have repaired CoA first and performed an intracardiac repair in 1 or 2 weeks.

Repeated two-dimensional echocardiography may be the procedure of choice in identifying the abnormal membrane in the left atrium and should be performed in any patient in whom this anomaly is suspected. The association of cor triatriatum, CoA, and VSD is a very uncommon but potentially repairable cause of congestive heart failure and death in infancy. Early accurate diagnosis aided by an awareness of this combination and prompt surgical correction, mostly by a staged approach, should yield excellent long-term results.

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Congenital Aneurysm of the Left Atrial Wall in Infancy

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A 5-month-old male infant with congenital left atrial aneurysm is reported. The youngest patient previously reported was 2½ years old. This case is unusual because the patient was an infant and because of the degree of mitral insufficiency and acute cardiac decompensation observed in the patient.

(Ann Thorac Surg 1990;49:476–8)

Isolated congenital aneurysmal dilatation of the left atrial wall is a rare condition. Life-threatening complications, including systemic embolization, serious arrhythmias, and severe congestive heart failure, may occur.

A 5-month-old infant born after an uncomplicated full-term pregnancy was transferred to our institution for evaluation of cardiac murmur and congestive heart failure requiring massive doses of dopamine and dobutamine (40 and 20 μg/kg/min, respectively). He was in his usual state of good health until age 5 months, when grunting respirations, diminished appetite, irritability, and fatigue gradually developed over a three-day period. Physical examination showed a 7.2 kg, irritable, well-developed male infant with a respiratory rate of 54/min and nasal flaring. Chest auscultation revealed diffuse bibasilar rales and a 3/6 holosystolic murmur at the apex with radiation over the entire precordium. The liver edge was palpable 3 cm below the costal margin. Initial chest roentgenogram showed cardiomegaly and pulmonary vascular engorgement. Arterial blood gases obtained on room air included a pH of 7.35, oxygen tension of 67 mm Hg, and carbon dioxide tension of 37 mm Hg. Electrocardiogram demonstrated normal sinus rhythm. Echocardiogram demonstrated a massively dilated left atrium with severe mitral insufficiency. Congestive heart failure was treated with digoxin, diuretic agents, dopamine, and dobutamine, and his hemodynamics stabilized. Subsequent cardiac catheterization and cineangiography confirmed the presence of a large aneurysm on the left atrium bulging beneath the heart and displacing the left ventricle anteriorly (Fig 1). Severe mitral regurgitation, but no other cardiac anomalies, was noted. After cardiac catheterization, the patient continued to have decompensated congestive heart failure requiring marked inotropic support. He was taken to operation on an urgent basis for left atrial aneurysmectomy and mitral valve repair or replacement as indicated.

Intraoperative exploration through a median sternotomy incision revealed the large aneurysm of the left atrial wall projecting posteroinferiorly (Fig 2). There was no pericardial defect. The aneurysm wall was extremely thin with a violaceous cast and visible blood swirling beneath its surface. The aneurysm was approximately four to five times the size of the left ventricle and did not involve the left auricular appendage. It did involve a 1-cm portion of the posteromedial commissure of the mitral valve annulus, producing marked annular dilatation. The mitral valve leaflets, papillary muscles, and chordal structures were intact and appeared normal. No thrombus was contained within the aneurysm sac. Injection of cold crystalloid solution through a left ventricular vent demonstrated a markedly regurgitant mitral valve. A limited DeVega annuloplasty was performed for approximately one third of the mitral circumference in the region of the posteromedial commissure, with marked reduction in mitral insufficiency (Fig 3). The large aneurysmal sac was resected, and the left atrial wall was closed in two layers (Fig 4). The child was sluggish at discontinuation of cardiopulmonary bypass, requiring large doses of inotropic agents, as was true preoperatively. However, he improved rapidly in the intensive care unit, with discontinuation of all inotropic support and extubation by the third postoperative day. Subsequent echocardiogram showed mild mitral prolapse with no mitral regurgitation. The left atrium remained moderately dilated, but no recurrent aneurysm was seen. He was discharged from the hospital 2 weeks postoperatively and continues to do well over a 4-year follow-up period. Repeat chest roentgenogram and echocardiogram at 4 years after operation are normal.

Comment

Left atrial aneurysms have been classified as either congenital or acquired. Although both are rare, acquired aneurysms are relatively more common and have been associated with conditions that chronically increase atrial pressure or weaken the atrial wall, such as rheumatic mitral valvular disease, tuberculosis, and syphilitic myocarditis. A congenital etiological process is supported by young age, lack of associated valvular abnormalities, and absence of histological demonstration of a specific degenerative disease in the atrial wall. Although mitral regurgitation was present, a congenital etiological process in our patient was supported by his young age and grossly

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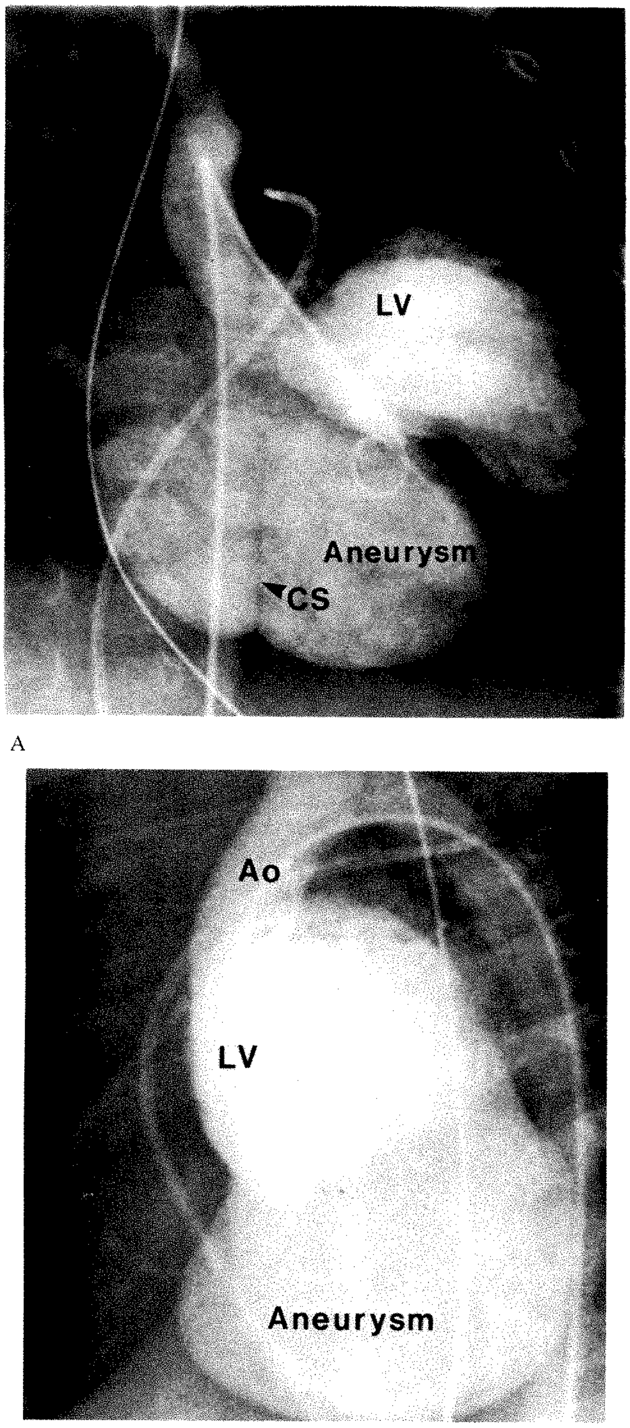

A

B

Fig 1. Left atrial aneurysm displacing the left ventricle as shown in the (A) right anterior oblique and (B) left anterior oblique projections. (Ao = aorta; CS = coronary sinus; LV = left ventricle.)

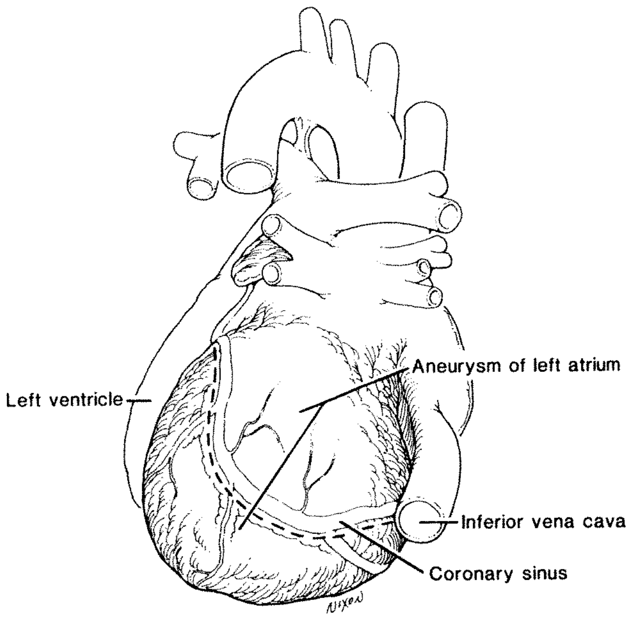

Fig 2. Coronary sinus is draped over aneurysmal left atrium.

normal mitral valve, except in the area involved by the aneurysm. These aneurysms far more frequently involve the atrial appendage than the atrial wall. We could find only 12 previous cases of isolated aneurysm of the left atrial wall since the original report by Semans and Taussig in 1939 [1–13]. The age range before the present case report was 2 to 55 years (mean, 18 years). Our patient is unusual because of the presence of isolated congenital aneurysm of the left atrial wall in infancy.

Congenital left atrial aneurysm most commonly is seen with supraventricular tachyarrhythmias, systemic embolization, or congestive heart failure. Congestive heart failure may be related to the space-occupying aneurysmal sac impeding pulmonary venous drainage, annular dilatation of the mitral valve due to left atrial enlargement, or marked deformity of the mitral valve annulus by the aneurysm sac itself. In our patient, the same pathological process that caused thinning and dilation of the left atrial wall also appeared to affect a limited portion of the mitral annulus, allowing it to dilate and cause severe mitral regurgitation.

Occasionally, a relatively asymptomatic patient may be shown by chest roentgenogram to have an abnormality, usually consisting of a prominent left heart border. The diagnoses to be excluded in such conditions are cardiac and other mediastinal tumors. Echocardiography should be performed and will demonstrate a large echo-free space in proximity to the left atrium. Echocardiogram, however, does not identify the origin of the aneurysm discretely, and it cannot distinguish between congenital

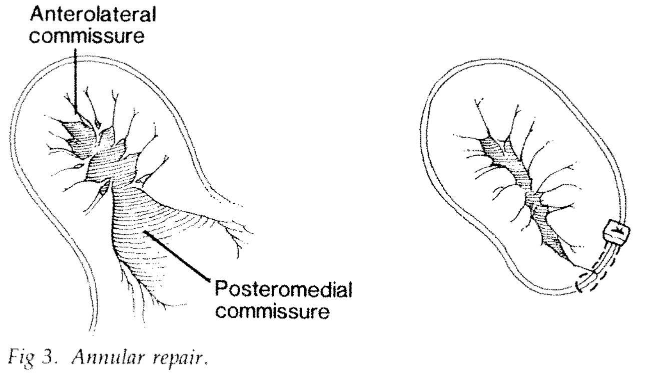

Fig 3. Annular repair.

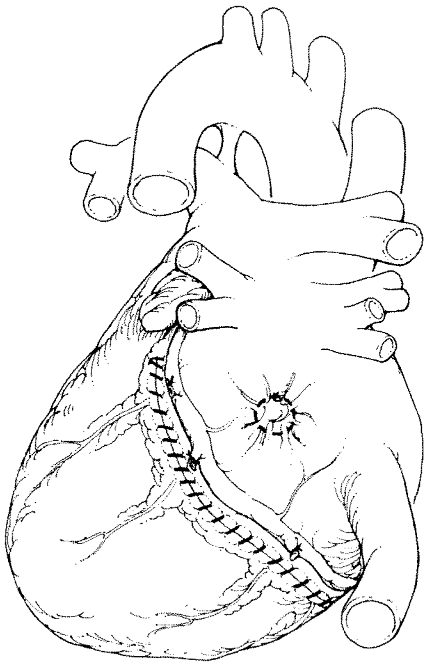

Fig 4. Operative repair included resection of the portion of the left atrial aneurysm below the coronary sinus and pursestring repair of the aneurysmal left atrium above the coronary sinus.

left atrial aneurysm and pericardial or other mediastinal cysts. Cardiac catheterization with cineangiography is generally accepted as the diagnostic study of choice for congenital left atrial aneurysm. Valvular disease and shunts can be evaluated and cardiac tumors ruled out by cardiac catheterization. Delayed emptying from the left atrial aneurysm sac may be demonstrated.

Due to the risk of life-threatening complications (including embolism, tachyarrhythmia, and severe congestive heart failure), aneurysm resection is indicated even for asymptomatic patients. Principles of operative management include use of cardiopulmonary bypass and minimal manipulation of the aneurysm sac before clamping the aorta to avoid systemic embolization. Aneurysms of the left atrial appendage without associated thrombus may be approached by simple ligation without cardiopulmonary bypass. Lesser degrees of mitral insufficiency are expected to resolve after aneurysmectomy. Mitral regurgitation of greater magnitude, particularly if the aneurysm involves the mitral valve apparatus, requires mitral valve repair or replacement.

The prognosis for congenital left atrial aneurysm after operative treatment is excellent. Only a single instance of recurrent supraventricular tachyarrhythmia has been reported [8], with no episodes of systemic embolization subsequent to operation [1–13]. Even the most severe manifestation of congestive heart failure reported in our patient has remained well compensated 4 years after operation.

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Multiple Free (Aorta–Coronary) Gastroepiploic Artery Grafting

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The use of in situ gastroepiploic artery grafts has been reported recently. In the present case, the in situ gastroepiploic artery was too short to graft both the diagonal and the obtuse marginal branches of the coronary arteries in a patient with diffuse coronary artery disease. The free (aorta–coronary) gastroepiploic artery graft was anastomosed to both arteries to form a Y graft.

(Ann Thorac Surg 1990;49:479–80)

A number of recent reports have attested that an internal mammary artery (IMA) graft to a coronary artery has a higher late patency rate than a comparable saphenous vein graft [1]. The IMA graft has gained prominence, and a number of innovative techniques are used to revascularize multiple coronary arteries using both IMAs. To gain versatility, bilateral, sequential, and free (aorta–coronary) IMA grafts have been performed [2]. The right gastroepiploic artery (GEA), a branch of the gastroduodenal artery, supplies the greater curvature of the stomach and, when appropriately harvested, is capable of easily reaching the posterior and lateral surfaces of the heart. Recently, the use of GEA for coronary artery bypass grafting has been described [3–6]. In the present report, we describe the use of a free GEA graft in a patient with diffuse coronary artery disease.

A 57-year-old man had a posterior myocardial infarction in 1980 and an anterior myocardial infarction in 1985. He had a history of diabetes since 1975. He was diagnosed as having Buerger's disease and thus had an amputation of the right leg in 1986. Because of progressive symptoms of angina, he underwent cardiac catheterization. Coronary angiography revealed total occlusion in the right coronary artery and the left circumflex coronary artery and severe lesions in the left anterior descending coronary artery and the diagonal branch of the left anterior descending coronary artery. The left ventriculograms showed severe diffuse hypokinesis and the ejection fraction was 30%.

The patient underwent coronary artery bypass grafting to the left anterior descending coronary artery and the diagonal coronary artery and the posterolateral branch of the left circumflex coronary artery. The saphenous vein was not usable for the grafts. The left IMA was hard and not well palpable and was decided not to be feasible for the graft. The median sternotomy incision was extended just below the midpoint between the xiphoid process and the umbilicus. The GEA was dissected and transected at its origin. Standard techniques of cardiopulmonary bypass with moderate hypothermia and cold potassium cardioplegic arrest were used.

The free GEA graft was divided into two segments. The graft was anastomosed to the obtuse marginal branch and the diagonal branch of the coronary arteries to form a Y graft (Fig 1). The coronary anastomoses were done with interrupted 7–0 silk sutures and the aortic anastomosis, with continuous 6–0 Prolene suture (Ethicon, Somerville, NJ). A continuous 7–0 Prolene suture was employed at the anastomoses between the GEAs. The right IMA was grafted to the left anterior descending coronary artery. All anastomoses were performed under aortic cross-clamping.

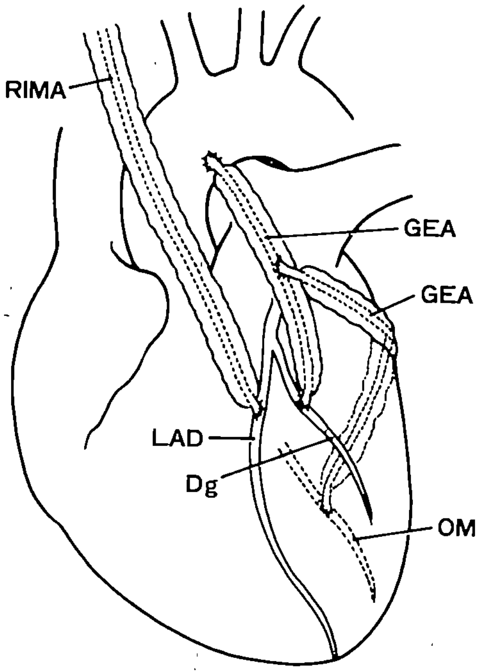

Fig 1. Anastomoses of free gastroepiploic artery (GEA) *to the diagonal* (Dg) *and obtuse marginal* (OM) *branches to form Y graft.* (LAD *= left anterior descending coronary artery; RIMA = right internal mammary artery.)*

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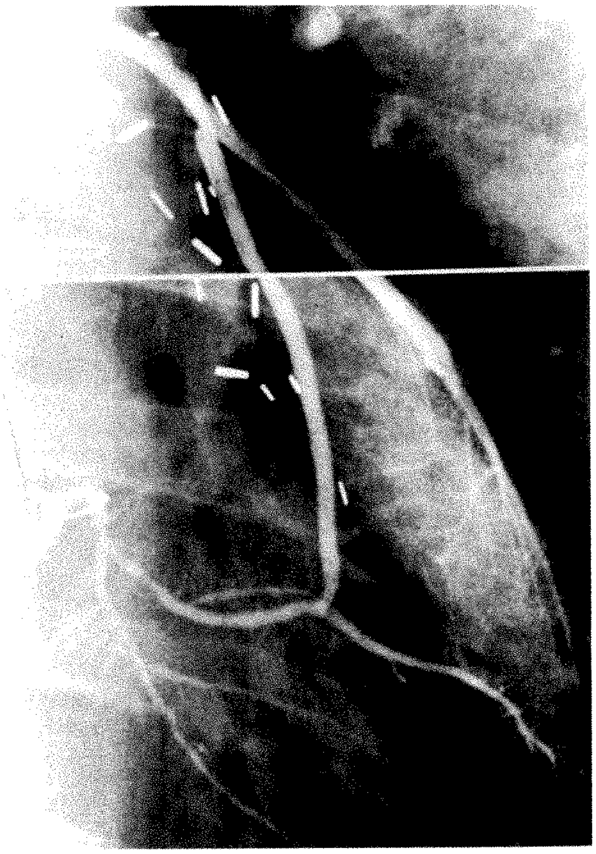

Fig 2. Coronary arteriograms in the right anterior oblique projection. The free gastroepiploic artery was grafted to the diagonal and obtuse marginal branches to form a Y graft.

In the postoperative coronary arteriography, all grafts were patent (Fig 2), allowing the patient to be discharged without symptoms of angina. Subsequently, gastroendoscopic examination was performed. The gastric mucosal blood flow was not disturbed in the area supplied by GEA according to the laser-Doppler method. The Congo red method did not reveal impairment of acid secretion in the area supplied by the GEA.

Comment

In the present case, the saphenous vein and the left IMA were not feasible for the graft to the coronary arteries. The in situ GEA was not long enough to graft both the diagonal coronary artery and the obtuse marginal branch. The GEA was transected at its origin and grafted to the obtuse marginal branch and the diagonal artery to form a Y graft.

Some questions remain. First, the long-term patency of the free GEA has not been documented. There have been several reports that the free IMA graft has relative immunity from atherosclerosis [2]. The long-term patency has to be observed in free GEA. Second, the stomach does not have a blood supply from the right GEA in the in situ GEA or free GEA graft operation. In the present case, blood flow and acid secretion were not impaired in the area supplied by GEA. However, the long-term gastrointestinal function or morbidity of the gastrointestinal tract has to be followed.

Wider use of this GEA graft may be indicated for revascularization. Not only is it an alternative bypass graft when more conventional conduits are absent or unsuitable, but it gives the cardiac surgeon the possibility of a third arterial coronary bypass graft in addition to the left and right IMA. Moreover, removing the GEA and using it in the aorta–coronary position increases the versatility of GEA grafting. As in the present case, multivessel grafting to the obtuse marginal branch and the diagonal branch to form a Y graft is feasible because of the length of GEA, which indicates that this technique could be applied to patients undergoing reoperation for vein graft failure and to patients with saphenous vein that is of poor quality. With further experience, the use of the free GEA graft operation might be justified on the basis of late patency, angina relief, and survival.

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Myocardial Abscess in a Patient With AIDS-Related Complex: Pericardial Patch Repair

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A hemophiliac with acquired immunodeficiency syndrome–related complex was seen with sepsis related to a ventricular septal abscess. The abscess was debrided and the septum was patched with a single layer of autologous pericardium. The patient recovered and survived 6 months before dying of acquired immunodeficiency syndrome. At autopsy, the septal patch was well healed with no evidence of recurrent endocarditis.

(Ann Thorac Surg 1990;49:481–2)

The acquired immunodeficiency syndrome (AIDS) is becoming increasingly common, especially in urban centers. In early 1989, there were over 85,000 cases of AIDS reported in the United States [1]. The approach to patients with AIDS or AIDS-related complex who require a cardiac operation is currently evolving [2]. One must consider the risks to medical personnel, the risks to the patient from cardiac disease, and the patient's life expectancy.

A 28-year-old male hemophiliac became ill with an intravenous line-related *Staphylococcus aureus* sepsis, secondary to factor VIII infusion for a spontaneous subdural hematoma. After a 2-week course of appropriate intravenous antibiotics, his sepsis recurred. A two-dimensional echocardiogram suggested the presence of a ventricular septal abscess (Fig 1). He was referred to our institution for surgical treatment.

With respect to the diagnosis of AIDS-related complex, the patient was serologically positive. His wife had converted to seropositivity 10 months before. The patient had a 6-month history of episodes of fever, malaise, and weight loss. He had cervical lymphadenopathy, and 4 months before he began showing symptoms, a pneumonia had developed that responded to empirical treatment with Septra (trimethoprim and sulfamethoxazole; Burroughs Wellcome, Research Triangle Park, NC). Although he did not fit the strict Center for Disease Control criteria for the diagnosis of AIDS, the prior pneumonitis with a presumed opportunistic pathogen is highly suggestive of the diagnosis.

At our hospital, he was a desperately ill-looking, febrile young man. After transfusion of cryoprecipitate to normalize his factor VIII level, he was taken to the operating room. After institution of standard cardiopulmonary bypass, the ventricular septum was explored through the aortic root and a right ventriculotomy. An indurated area was noted high in the septum. This was incised and purulent necrotic material was evacuated. A thorough debridement of the abscess cavity left a defect in the septum approximately 2 × 3 cm. This was patched with a single layer of autologous pericardium sutured with a continuous running 4-0 polypropylene suture to the endocardium of the ventricular septum from the left side. The right side of the septum was left open to drain into the pulmonary circulation. The patient had coagulopathy and bled excessively, requiring transfusion of packed cells, platelets, and clotting factors. His postoperative course was remarkably smooth. He required digitalization for supraventricular tachycardia on the first postoperative day. He was extubated within 24 hours. A new permanent right bundle-branch block developed. A postoperative echocardiogram is shown in Figure 2.

The patient was discharged after completion of a 4-week course of antibiotics. He remained alive and in a reasonable state of health until 6 months postoperatively, when he once again became ill with pneumonia and ultimately died. An autopsy was performed and demonstrated patchy pneumonitis secondary to pneumocystitis and cytomegalovirus infection. The adrenal glands showed a severe necrotizing adrenalitis due to cytomegalovirus infection, which probably contributed to the patient's death. In addition, there was evidence of active hepatitis with early cirrhosis. Examination of the heart showed that the autologous pericardial patch had been incorporated into the septum as an area of extensive fibrosis. There was no evidence of aneurysm formation, dehiscence, or continued infection.

Comment

Little information is available on patients with AIDS or AIDS-related complex undergoing open heart operations with cardiopulmonary bypass. We used standard blood precautions and bypass techniques. There is a theoretical increased risk of postoperative infection because the derangements in the immune system as a consequence of bypass are potentially amplified in these patients with an already altered immune status. There is some concern that patients who are seropositive for human immunodeficiency virus infection are at increased risk of developing the clinical picture of AIDS after institution of cardiopulmonary bypass (D. Hill, personal communication). There is no way of knowing whether operation hastened this

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patient's death of AIDS; however, it was clear to us that any extended survival in his preoperative septic state was extremely unlikely. We believe that his evolution toward AIDS was likely to happen in the same time frame without operation.

Autologous pericardium has a proven track record in reconstruction of the aortic root [3, 4]. The use of autologous pericardium in reconstruction of the left ventricular wall is somewhat controversial. There have been reports [5] of aneurysm formation after patch repair of ventricular septal defects in children with autologous pericardium. We have reported our experience with reconstruction of the mitral annulus [6] and the left ventricular wall using autologous pericardium [7]. That experience consisted of 25 patients, 15 with infective endocarditis complicated by abscess formation, and 10 with noninfectious disorders. Our follow-up was relatively short, but we had excellent results with no reinfection, prosthetic dehiscence, patch dehiscence, or patch aneurysms. There were three deaths in that series, all related to the preoperative morbid states of the patients [7].

The probability of survival with AIDS for varying periods of time has been calculated in a variety of patient populations in New York City [8]. These data and similar information on life expectancy in various subgroups of AIDS patients may help surgeons recommend treatment options to these patients. The diagnosis of AIDS is not an absolute contraindication to cardiac operation. One must make the judgment to proceed with operation based on several factors including a realistic appraisal of life expectancy with and without operation. As newer methods of controlling this disease become known, cardiac operations may become easier to recommend to these patients.

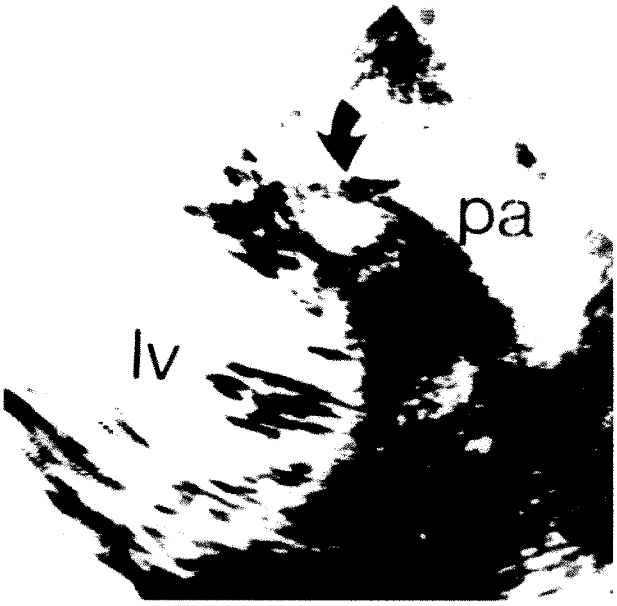

Fig 1. Two-dimensional echocardiogram demonstrating lucent area high in ventricular septum, pointing into right ventricular outflow tract (arrow). (lv = *left ventricle;* pa = *pulmonary artery.)*

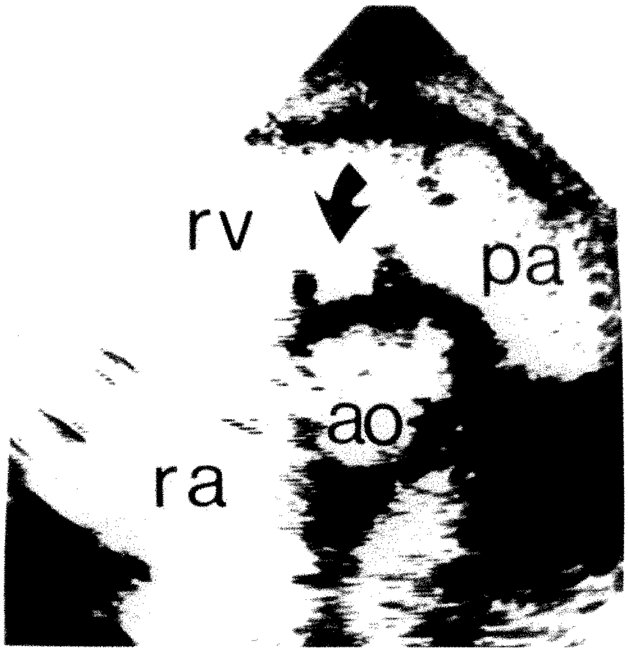

Fig 2. Two-dimensional echocardiogram 1 week postoperatively demonstrating old abscess cavity (arrow). The cavity is closed on the left ventricular side with autologous pericardium and is open on the right ventricle (rv) *side to drain into the pulmonary circulation. No patch leak or bulging of the patch could be demonstrated.* (ao = *aorta;* pa = *pulmonary artery;* ra = *right atrium.)*

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Coronary Artery Bypass in a 15-Year-Old Girl With Pseudoxanthoma Elasticum

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A 15-year-old girl with pseudoxanthoma elasticum and associated severe coronary artery disease underwent double coronary artery bypass using left internal mammary artery and saphenous vein. Preoperatively the patient had life-threatening syncope and positive treadmill test results. The postoperative course was uneventful, and the patient has been doing well for 3 years. Pseudoxanthoma elasticum is a rare disease that can cause premature coronary arterial obstructive disease in children and adolescents.

(Ann Thorac Surg 1990;49:483–5)

Pseudoxanthoma elasticum (PXE), also known as Groenblad-Strandberg syndrome, is a rare, autosomal-recessive, heritable disorder of connective tissue characterized by deranged elastic fiber metabolism and synthesis. Systemic organs such as skin, mucous membranes, eyes, heart, peripheral blood vessels, and gastrointestinal tract may be involved in this disease. Cardiovascular manifestations of PXE can be life-threatening and require surgical intervention.

A 15-year-old girl suffered a syncopal attack during exercise and was referred to a hospital. Her family history revealed that a paternal aunt had died suddenly at 8 years of age. On her arrival in the emergency room, the patient was in respiratory arrest. Blood pressure fell below 50 mm Hg, but recovered to normal with cardiopulmonary resuscitation.

Two weeks later, a treadmill test was performed and revealed ST depression in leads II, III, aV$_F$, and V$_2$ to V$_6$. Subsequently, she was transferred to the Heart Institute of Japan for further examination. Physical examination disclosed a yellowish papular skin rash in the lateral neck, axilla, periumbilical and inguinal regions. Typical angioid streaks were not seen in the optic fundi, but the mottled appearance was compatible with an early stage of PXE. A 24-hour electrocardiogram revealed sporadic premature ventricular contraction and ST segment depression during walking and excretion. Coronary angiography demonstrated 90% stenosis of proximal left anterior descending and left circumflex coronary arteries with poor distal runoff and 99% stenosis of the posterior descending coronary artery (Fig 1). Left ventriculography was normal, with an ejection fraction of 0.60. Cardiac index was normal (3.8 L/min/m^2) and left ventricular end-diastolic pressure was slightly elevated to 13 mm Hg. T1-201 scintigraphy showed perfusion defects in the anterior and high anterolateral segments induced by exercise. Celiac angiogram also showed elongated tortuous arteries, particularly in the stomach. These coronary findings and the life-threatening clinical course indicated that coronary bypass grafting was necessary for this young patient.

In December 1985, using standard cardiopulmonary bypass with systemic hypothermia and cold crystalloid cardioplegia, double coronary artery bypass grafting was performed; the left internal mammary artery (IMA) was grafted to the left anterior descending coronary artery and the saphenous vein, to the posterior descending coronary artery. It was thought that the right internal mammary artery, less than 1 mm in diameter, was too small and short to be used. Histological study of an IMA specimen revealed calcified foci in the media 50 to 100 μm in diameter. The specimen of the ascending aorta showed intimal fibrosis, focal fibrosis in the media, and atrophy of smooth muscle. The saphenous vein was histologically normal. The postoperative course was uneventful until postoperative day 5, when massive gastric bleeding occurred. Conservative therapy, including hemostatic drugs, antacids, gastric lavage, H$_2$ receptor antagonist, fibrinogen, and Sengstaken-Blakenmore tube, was applied, but it was unsuccessful. Blood pressure dropped to 50 mm Hg with massive hemorrhage, and the total amount of blood transfusion reached 4,200 mL. Emergent gastroscopy was performed and active bleeding from a dilated mucosal artery in the gastric fundus was found. This bleeding artery was coagulated using electrocautery through the endoscope. The patient convalesced progressed without complication after this episode.

Postoperative coronary angiography was performed after 3 months and revealed that the left IMA was patent but the saphenous vein graft was occluded (Fig 2). The patient was discharged without any symptoms of ischemia and has been asymptomatic for 3 years.

Comment

Although PXE is a relatively uncommon disease that has no characteristic clinical course, acute catastrophic events

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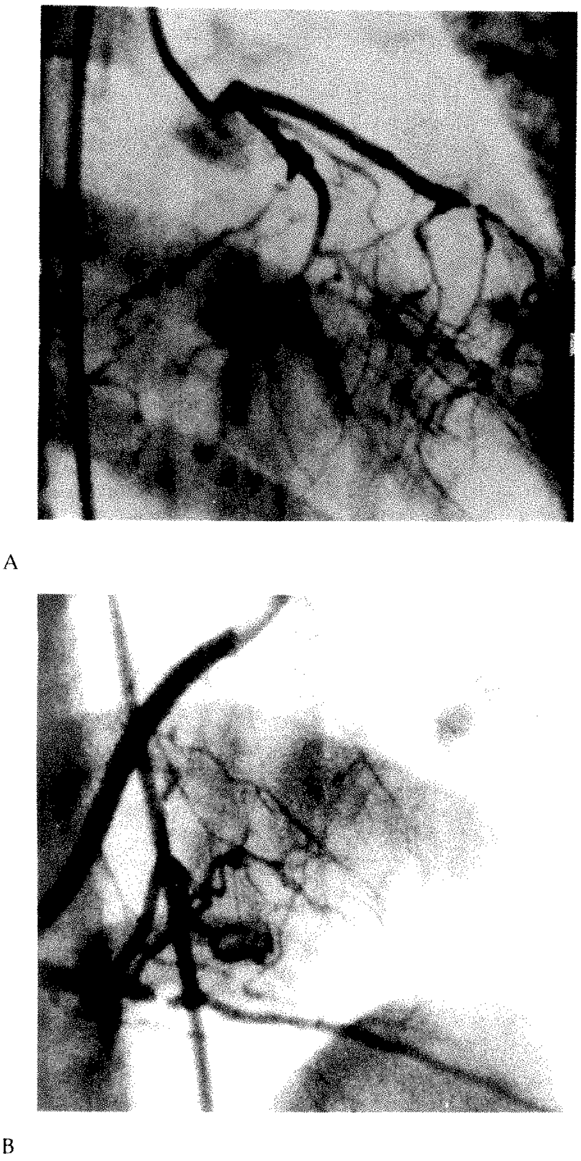

Fig 1. Coronary angiography demonstrated (A) 90% stenosis of proximal left anterior descending artery and left circumflex artery with poor distal runoff and (B) 99% stenosis of posterior descending and right coronary artery.

such as coronary insufficiency [1, 2], sudden death [3], and gastrointestinal hemorrhage [4] have been reported. In most clinical cases, the cardiac lesions are variable [5, 6] and may remain undetected.

Bete and associates [7] reported an 18-year-old woman with a 7-year history of angina due to PXE who underwent successful triple coronary artery bypass grafting using saphenous vein grafts. We previously demonstrated that early occlusion rate of saphenous vein grafts is significantly higher in pediatric patients with Kawasaki disease than in adult patients [8]. The use of IMA is the best choice for pediatric coronary bypass grafting if its size is appropriate. In our patient, despite intensive use of hemostatic agents for gastric bleeding, the IMA was patent for 3 months after operation, whereas the saphenous vein was occluded. However, elaborate long-term follow-up should be undertaken, because foci of calcification were detected in the media of the IMA. Gastrointestinal bleeding can occur as a serious perioperative complication in patients with PXE, and emergent gastroscopy was very effective method to be considered.

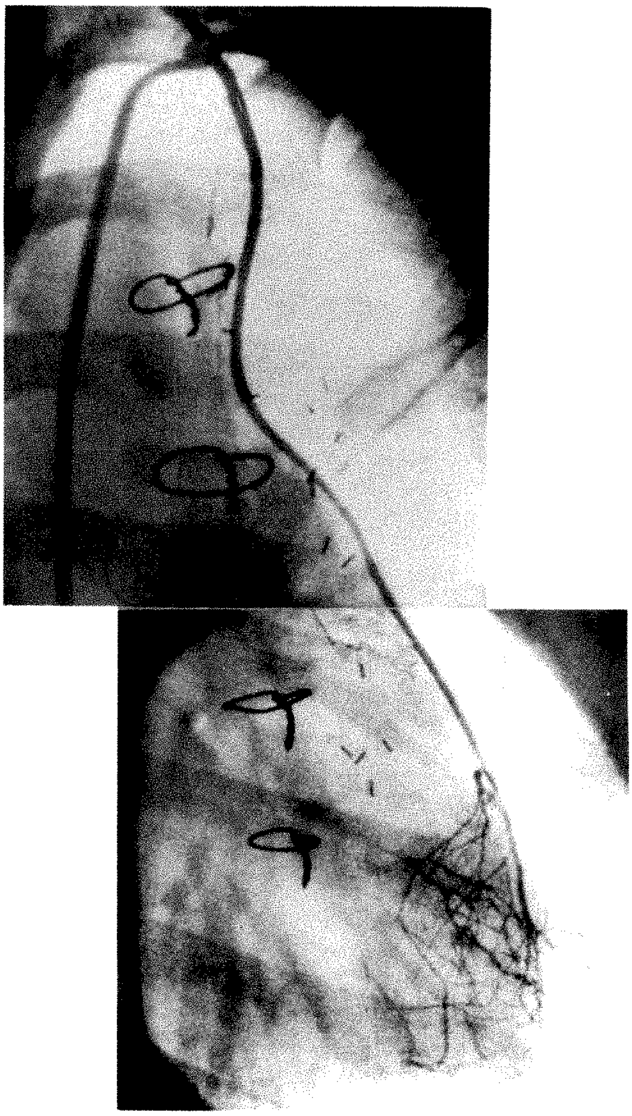

Fig 2. Postoperative coronary angiography demonstrated patent internal mammary artery graft.

In summary, PXE should be considered, along with Kawasaki disease and homozygous familial hyperlipidemia, a condition in which coronary revascularization may be required during childhood or adolescence.

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INVITED COMMENTARY

Apparently, the patient with pseudoxanthoma elasticum in whom I performed coronary bypass in 1971 is the only previously reported patient operated on for this rare condition. That patient, an 18-year-old girl who had experienced angina since age 11 years, had triple bypass with vein grafts (Fig 1). Angina recurred about 8 years later, but thallium stress test results were negative at 11 years postoperatively. Cardiac catheterization in 1985, 14 years after operation, revealed both vein grafts to three vessels to be patent and without evidence of disease, with good runoff. There was progression of occlusive disease in the native circulation (Fig 2). Dr Herbert J. Levine has provided follow-up to the effect that she is alive today but not particularly well, with intermittent claudication of both upper and lower extremities, some congestive heart failure symptoms, and angina. She has had four healthy children.

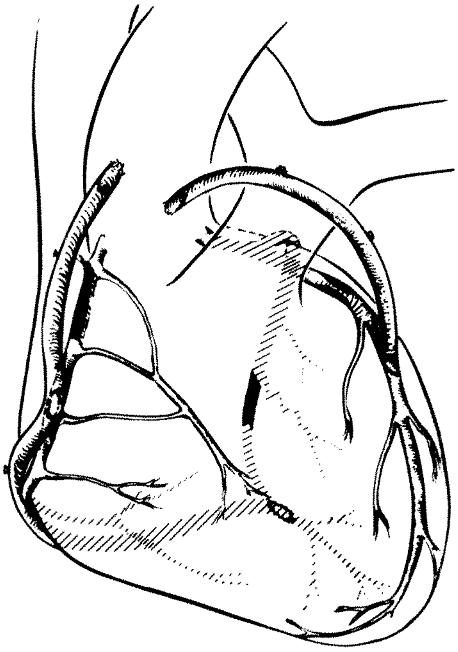

Fig 1. Coronary anatomy and vein bypass. Right coronary and circumflex arteries were occluded and the left anterior descending coronary artery was stenotic. A tandem graft served the right and distal circumflex arteries.

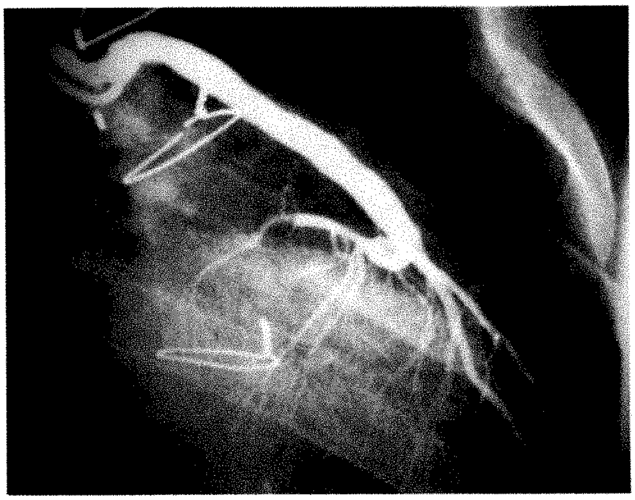

Fig 2. Left anterior descending coronary artery graft without evidence of disease and good runoff at 14 years. The tandem graft was similarly patent, free of disease, and with good right and circumflex runoff.

Although we were using internal mammary artery grafts in 1971, we consciously chose vein for conduit because of the known predilection for arterial degeneration in both upper and lower extremities in this condition and, by inference, in the mammary artery system. It is interesting that a biopsy specimen of internal mammary artery in this report by Nishida and colleagues showed extensive intramural calcification, similar to that documented in the occluded right coronary artery of our patient. Therefore, I take issue with Nishida and associates that the internal mammary artery is the conduit of choice in this rare condition, while commending them for their aggressive surgical approach and the good result.

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Three-Dimensional Image Reconstruction for Planning of a Complex Cardiovascular Procedure

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A rare left subclavian artery aneurysm associated with a congenital arch anomaly was difficult to visualize using standard radiographic techniques. Three-dimensional computer imaging produced a clear depiction of this unusual anatomy and simplified the preoperative planning.

(Ann Thorac Surg 1990;49:486–8)

Aneurysms of the subclavian artery are uncommon, and those associated with aortic arch anomalies are quite rare. Twenty-seven cases of right aberrant subclavian artery aneurysms have been reported in the English-language literature [1, 2], and aneurysms of an aberrant left subclavian artery arising from a right aortic arch are even more rare. We recently treated a patient with this anomaly and found preoperative planning to be challenging because of the lack of reported information on this rare aneurysm and the difficulty in obtaining a clear visualization of the anatomy using standard radiographic studies. Three-dimensional computer imaging clarified the important anatomical relationships considerably, and the ability to rotate the images in space according to our specifications simplified preoperative planning.

On a routine chest radiograph, a 41-year-old man was found to have a new left superior mediastinal mass. Previous studies had demonstrated a right aortic arch with an aberrant left subclavian artery. The patient complained of mild exertional wheezing and occasional dysphagia but was otherwise free of symptoms. The physical examination was normal except for a diminished left radial pulse.

Computed chest tomography demonstrated an aneurysm of the proximal left subclavian artery, but its point of origin from the aortic arch was ill-defined. Arteriography confirmed the 6-cm vascular lesion and indicated that the aneurysm arose from the posterior aspect of the arch with extension just to the left of midline. This information indicated that proximal control of the aneurysm was apt to be quite difficult, so to define the proximal subclavian in as much detail as possible, a nuclear magnetic resonance scan was performed. The coronal sections from this study suggested that the aneurysm began 2 to 3 cm left of the midline and that the subclavian artery arose from the left posterolateral aspect of the distal (right) aortic arch.

The operative approach to this vascular lesion was difficult to plan because of the slightly differing interpretations of the origin of the aneurysm. To further clarify the information from these standard radiographic studies, three-dimensional computer modeling using these studies was carried out. The reconstructed three-dimensional images demonstrated clearly that the aneurysm could be approached through a left posterolateral thoracotomy incision and that the need for additional exposure would be unlikely (Figs 1–3).

The patient was explored through the bed of the resected fourth rib using a left posterolateral thoracotomy incision. The left subclavian artery originated from the left posterolateral arch and was of normal caliber from its origin to a point 3 cm distally, where the aneurysm arose.

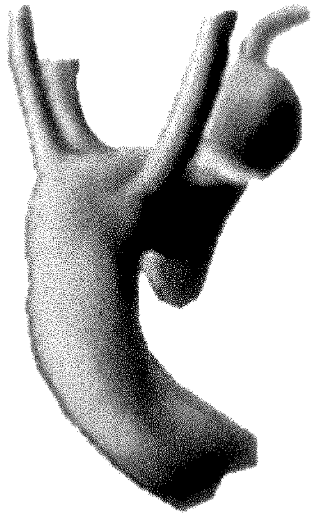

Fig 1. Computerized reconstruction (anterior view). The first branch from the aorta is the left common carotid artery, followed in order by the right common carotid, right subclavian, and the (aberrant) left subclavian artery. The aneurysm is identified, but its origin is obscure in this view.

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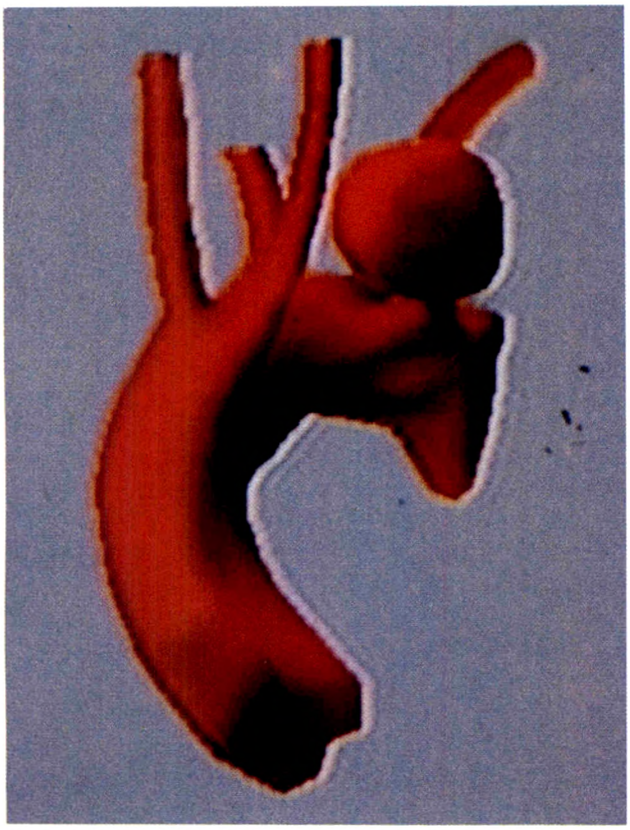

Fig 2. *Computerized reconstruction (left lateral view). The image in Figure 1 has been rotated to provide a view that one would anticipate from a left posterolateral thoracotomy incision. This showed the origin of the aneurysm very well and confirmed that proximal control could be obtained through the left thoracotomy incision.*

A complete vascular ring was formed by a large ductus that extended from the proximal subclavian artery to the left pulmonary artery. Figure 4 shows a line drawing of the anatomical structures of importance in this procedure.

The ductus was divided to allow full exposure and control of the proximal subclavian artery. The aneurysm was 6 cm in diameter and was characterized by a surprisingly narrow neck (3 cm). Distal control of the subclavian artery was obtained, the aneurysm was excised, and the subclavian artery was reapproximated without the use of a bypass graft.

There were no postoperative complications, and the patient was discharged six days after the procedure.

Comment

Subclavian artery aneurysms are uncommon vascular lesions that should be resected in all patients having an acceptable operative risk [3]. Aneurysms associated with arch anomalies have been encountered only rarely but should be subject to the same aggressive treatment [1, 4]. In the recent review by Esposito and associates [1], 5 of the 10 patients that did not undergo operation died of spontaneous rupture of the aneurysm. The operation carries a surprisingly high risk, with an operative mortality of 18% (3/17).

Variations in the anatomy of aortic arch anomalies coupled with the anatomical distortion produced by the aneurysm itself may make the interpretation of standard radiographic studies somewhat difficult. In our patient, the aberrant left subclavian artery arose from the left side of the arch rather than the right, as is usually the case. Additionally, the ductus branched not from the arch, but from the proximal left subclavian artery, which made radiographic identification of the proximal subclavian more complicated. Three-dimensional reconstruction of the mediastinal structures condensed this information to provide a clear visual concept of the anatomy for our preoperative planning.

Computer reconstruction is based on the two-dimensional images of standard radiographic studies. The important structures from these standard images are traced from each "slice" of the study and are sequentially entered into a computer program for storage into memory. The computer software will then digitize that information, so that a mathematical smoothing and surfacing function can be used to produce three-dimensional images that can be rotated about any axis to reveal areas of particular interest. Computer graphics technology is rapidly improving, and this type of soft tissue reconstruction should soon become available in most major medical centers. The

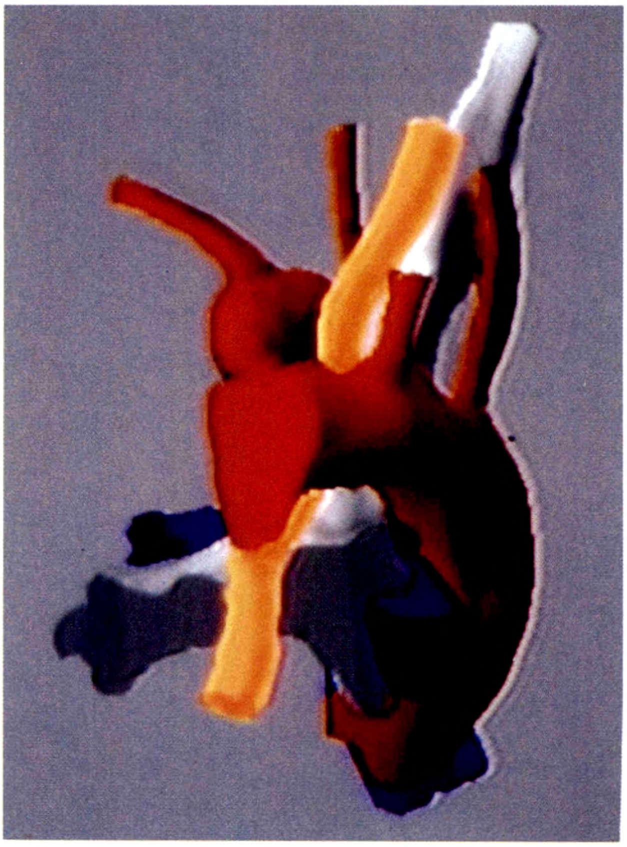

Fig 3. *Computerized reconstruction (posterior view). The relationship of the tracheobronchial tree* (gray), *esophagus* (orange), *and pulmonary artery* (blue) *can be seen. The cause for dysphagia in this patient is apparent from the esophageal distortion produced by the aneurysm.*

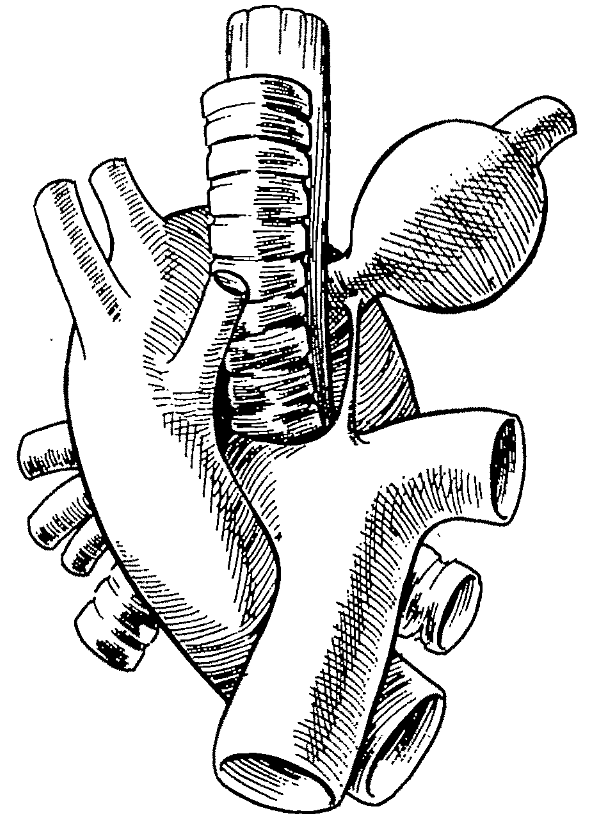

Fig 4. The vascular anatomy seen at the time of operation. In fact, the aneurysm was more closely applied to the esophagus, but for clarity, the proximal neck of the aneurysm has been reflected posteriorly to illustrate the ductus.

time required is dependent on the sophistication of the software, but is generally in the range of only a few hours.

Standard preoperative radiographic studies allow one to appreciate two-dimensional spatial relationships, but the anatomy of rare anomalies may be difficult to visualize in three-dimensional perspective. Standard radiographic studies are, of course, all that are really necessary for adequate planning, but three-dimensional computer reconstruction may crystallize the information from standard studies to make operative planning easier. When confronted with an unusual anomaly such as the one presented here, the ability to rotate the reconstructed image may be particularly helpful in illustrating subtle anatomical relationships. With the sophisticated level of computer support available in most major medical centers, this technology is now at our disposal. Perhaps it might be considered to facilitate the planning of especially challenging cardiovascular operations.

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Repair of the Calcified Ventricular Aneurysm

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A technique is described for repairing calcified ventricular aneurysms using internal repair rather than excision. This technique avoids distortion of the ventricular cavity and gives a good functional result. External buttresses, which can be a source of infection, are unnecessary for this repair.

(Ann Thorac Surg 1990;49:489–90)

Surgical repair of postinfarction left ventricular aneurysm has become a standard and frequently performed procedure, yet techniques of repair have varied widely. Formerly, emphasis was on excision [1]. Recently, however, the concept of excising the aneurysm, with or without a patch repair of the interventricular septum followed by linear repair of the ventriculotomy, has been questioned. Usually when a ventricular aneurysm is excised, the ventricle is distorted and the efficiency impaired, providing a less than optimal functional result. Calcified aneurysms are especially difficult to repair by excision, and results have been poor. In many instances, my colleagues and I, like others, have avoided operating on calcified lesions altogether, because the paradoxical contraction pattern present in noncalcified lesions is not present and the left ventricular function is not always seriously impaired (Fig 1A).

Recently, we have used a technique of internal repair of ventricular aneurysms that we have called endoaneurysmorrhaphy [2, 3]. The concept, originally suggested by Rudolph Matas for repair of arterial aneurysms [4], has proved to be a satisfactory method for repairing difficult, calcified ventricular lesions.

Technique

The usual median sternotomy incision is made with appropriate cannulation of the heart for cardiopulmonary bypass. During moderate hypothermic bypass, cardioplegic solution is injected into the ascending aorta. The large bone needle is left in place for aspiration.

The aneurysm is mobilized and dissected from the pericardial adhesions. The apex of the heart is elevated. Using a scalpel and heavy scissors, a ventriculotomy is made through the calcified wall lateral and parallel to the interventricular groove (Fig 1B). Upon internal examination, the transition zone between healthy myocardium and scarred tissue is identified adjacent to the calcified zone (Fig 1C). An elliptical patch of woven Dacron fabric is fashioned in the appropriate size to exclude the aneurysm and to restore the estimated normal diastolic volume of the left ventricle. The patch is sutured around the circumference with a continuous 2-0 or 3-0 monofilament polypropylene suture (Fig 1D). The patch should extend under but not into the ventriculotomy.

Dense calcification may make repair of the ventriculotomy incision difficult. Partial debridement and fragmentation of the margins can be done to permit repair with a continuous 2-0 or 3-0 polypropylene suture. Buttresses of felt or other material are seldom necessary, because the suture line is not subjected to intracavitary ventricular pressure (Fig 1E).

Appropriate myocardial revascularization is then performed. In most instances, the previously occluded left anterior descending coronary artery will be recanalized in a manner that is suitable for bypass with an internal mammary artery.

Comment

Most calcified ventricular aneurysms are chronic. The left ventricle is able to adapt to the presence of the noncontractile sac because the sac is not distensible, as it is in other aneurysms. Thus, the paradoxical contraction pattern seen with ventricular aneurysms is usually not present. Nevertheless, the blood flow and ejection pattern of the ventricle are still disturbed and impaired. During the systolic and diastolic phase, blood swirls around, and residual blood remains after each cardiac cycle (Fig 1A). Thrombosis resulting from stagnation is common.

Calcified ventricular aneurysms often have dense adhesions to the pericardium, most likely a result of early transmural necrosis. Fixation of the cardiac apex further impairs left ventricular function. Therefore, mobilizing the calcified aneurysm from the adhesions also improves left ventricular function by permitting torsion during the cardiac contraction cycle.

Our experience with ventricular aneurysms repaired using this concept has revealed that the customary buttresses of either Teflon or polyester felt are unnecessary [1]. Furthermore, the surface anatomy of the heart is preserved and the possibility of subsequent infection of the foreign buttressing material is eliminated. Other types of buttresses such as autologous pericardium [5] or absorbable material are also unnecessary.

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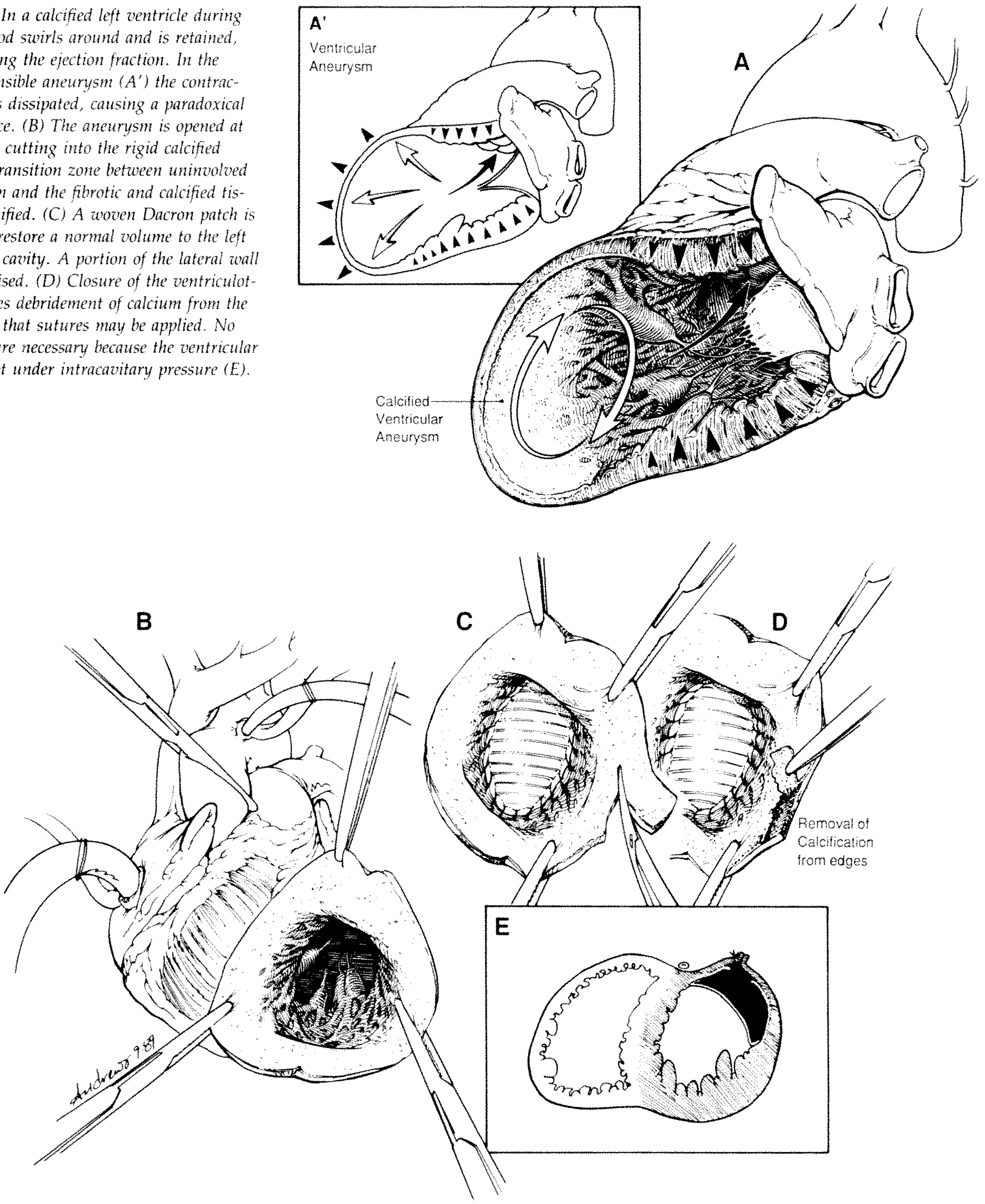

Fig 1. (A) In a calcified left ventricle during systole, blood swirls around and is retained, thus reducing the ejection fraction. In the usual distensible aneurysm (A') the contraction force is dissipated, causing a paradoxical ejection force. (B) The aneurysm is opened at the apex by cutting into the rigid calcified wall. The transition zone between uninvolved myocardium and the fibrotic and calcified tissue is identified. (C) A woven Dacron patch is tailored to restore a normal volume to the left ventricular cavity. A portion of the lateral wall may be excised. (D) Closure of the ventriculotomy requires debridement of calcium from the margins so that sutures may be applied. No buttresses are necessary because the ventricular repair is not under intracavitary pressure (E).

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The Killingbeck Pediatric Lung Retractor

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A new series of lung retractors has been designed for use in patients ranging from premature infants to large children. Their unique shape, low profile, and light weight affords excellent exposure with a minimum of trauma to tissues.

(Ann Thorac Surg 1990;49:491)

Excessive retraction and compression of lung caused while gaining exposure to the hilum of the lung may compromise ventilation in small children. Because retractors previously available have not enhanced this process, the Killingbeck pediatric lung retractor was designed to overcome such problems.

Design

The Killingbeck retractor was designed to imitate a hand. It has splayed fingers that maintain retraction of all required lung, not allowing the periphery to "spill" over the edges of the retractor (Fig 1). The length of the fingers reaches to just short of the hilum. The "palm" of the retractor is concave, thus minimizing compression of lung tissue, allowing maximum ventilation intraoperatively. The retractor is available in nine sizes for use in a range of children from premature infants weighing 700 g to teenaged children. All sizes are lightweight; the smaller three are made of titanium, and the others are made of drilled steel.

Comment

Mr D. R. Walker, a consultant cardiothoracic surgeon, designed the retractors a year ago and has used them in most of the 150 thoracotomies performed since then. When the retractors are used, a wet single thickness of swab is placed between them and the lung to prevent slip of the retractors out of the chest cavity. We use the smaller three sizes most often, because most of our patients are children aged less than 3 years. The smaller sizes fit easily into the smallest chest. They can be used singly or combined when used in larger children.

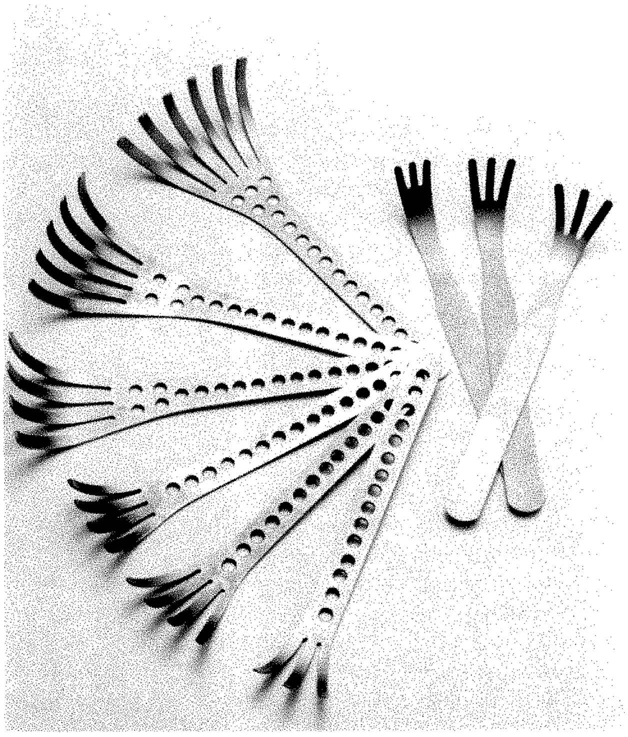

Fig 1. Variably sized Killingbeck retractors for use in infants and children.

The three titanium retractors have malleable handles, but we have never needed to alter their shape. The design enables an assistant to keep his or her hand and the retractor handle well out of the surgical field. Furthermore, the larger six retractors, which are not malleable, have not been found lacking; on the contrary, the shape of the retractors has proved very convenient, comfortable, and practical.

We use Killingbeck retractors routinely and have had no complications. We highly recommend them to pediatric thoracic surgeons as a tool of great usefulness.

Killingbeck retractors are available from Thackray Surgery, a division of F. Thackray Ltd, Leeds Division, Shire Oak St, Leeds LS6 2DP, England.

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Total Anomalous Pulmonary Venous Connection: Surgical Repair With a Double-Patch Technique

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A double-patch technique has been used to repair total anomalous pulmonary venous connection in 35 patients (mean age, 4.9 months; mean weight, 4.2 kg). In all patients with supracardiac or subdiaphragmatic type of total anomalous pulmonary venous connection, repair has been accomplished by enlarging the "new" left atrium. There were three early deaths (3 of 35 = 8.6%) and no late deaths in a mean follow-up of 30 months (3 to 71 months). We propose this double-patch technique as an alternative surgical option for total anomalous pulmonary venous connection.

(Ann Thorac Surg 1990;49:492–4)

Several surgical approaches [1–5] have been reported to repair total anomalous pulmonary venous connection (TAPVC). The problem of the left atrial size in patients with TAPVC has been considered in the literature [1, 3, 5], but only one report proposed a surgical technique aiming to enlarge the left atrium (LA) during repair [1]. We reviewed our experience with repair of TAPVC using the double-patch technique, adopted to create a large left atrial chamber in all patients with supracardiac or subdiaphragmatic type of TAPVC.

Material and Methods

Patients

From July 1983 to April 1989 35 patients with a mean age of 4.9 months (range, 5 days to 2 years) and a mean weight of 4.2 kg (range, 2.2 to 12.0 kg) underwent surgical repair of TAPVC. Twenty-two (62.9%) were aged less than 3 months. The type of TAPVC was supracardiac in 16 patients, coronary sinus in 12, subdiaphragmatic in 5, and mixed in 2. Associated cardiac lesions were patent ductus arteriosus in 8 patients, ventricular septal defect in 2, and partial atrioventricular septal defect in 1. Patients with right or left isomerism were excluded from this study. The diagnosis was based on echocardiography in 10 patients (28.6%) and on cardiac catheterization with angiography in 25.

Surgical Technique

The surgical procedure was performed during deep hypothermia and circulatory arrest. In all patients with supracardiac or subdiaphragmatic type of TAPVC, immediately after cardiac arrest, the right atrium was opened through a transverse incision beginning on the anterior wall and extending through the crista terminalis to the back wall of the LA. A ligature was tied on the tip of the left auricular appendage for leftward retraction to improve the intracardiac exposure. The common pulmonary venous sinus was longitudinally opened, with the right end of this incision reaching the bifurcation of the common pulmonary venous sinus at the right hilus. About two thirds of the common pulmonary venous sinus was anastomosed to the posterior opening of the atrial wall; the one third in correspondence with the right bifurcation was anastomosed to the base of a heterologous pericardial "external" patch, enlarging the "new" left and right atrial walls. The pulmonary venous return was deviated to the mitral valve by using a Teflon fabric "internal" patch constituting the new interatrial septum: the medial portion of this internal patch was sutured along the fossa ovalis, and the lateral portion was anastomosed to the middle internal aspect of the pericardial external patch used as new atrial wall (Fig 1). By shifting to the right the new interatrial septum, we substantially enlarged the new LA, including the sinus intercavarum. Indeed, the new LA remained delimited posteriorly by the posterior wall of the common pulmonary venous sinus, laterally by the pericardial external patch, and anteriorly by the Teflon fabric internal patch. The remaining portion of the external patch was anastomosed to complete the closure of the right atrium. Reperfusion, rewarming, and weaning from cardiopulmonary bypass were performed routinely. The persistent left vertical vein was ligated.

In patients with TAPVC in the coronary sinus, after incising the roof of the coronary sinus with or without enlargement of the atrial septal defect, we accomplished repair by deviating the coronary sinus to the LA using a Teflon fabric patch. Associated procedures were patent ductus arteriosus closure in 8 patients, VSD closure in 1 patient, pulmonary artery banding in 1, and suture of mitral cleft in 1.

Results

There were three hospital deaths (8.6%) due to intraoperative bleeding from laceration of the ascending aorta in a neonate, to residual ventricular septal defect in a child

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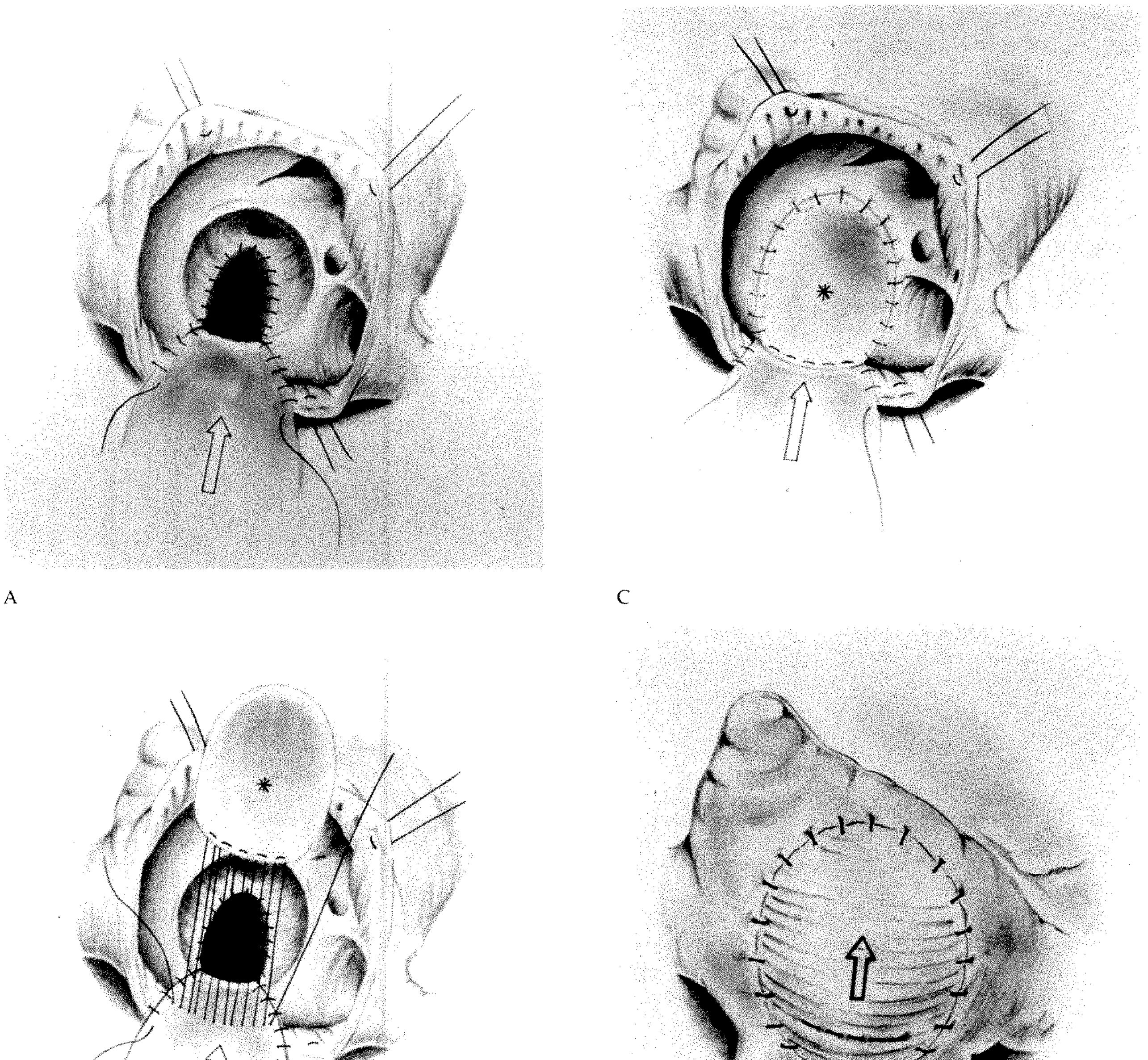

Fig 1. (A) The anastomosis of the common pulmonary venous sinus to the atrial wall and to the external pericardial patch (arrow) *is performed. (B) Suture of the internal patch of Teflon fabric (*) to the internal aspect of the pericardial patch is performed next. (C) Suturing of the new interatrial septum is completed. (D) Final result.*

with multiple ventricular septal defects discovered at autopsy, and to the desperate preoperative condition in a neonate with Sturge-Weber syndrome and esophageal atresia. All survivors are in good condition after a mean follow-up of 30 months (range, 2 to 71 months).

Comment

Experimental studies showed that (1) a decrease in atrial volume of more than 50% results in a significant reduction in cardiac output and (2) cardiac performance is markedly improved by increasing atrial compliance while maintaining constant ventricular contractility [3].

These factors, combined with the preoperatively observed small size of the LA in patients with TAPVC, has long made the possibility of LA enlargement by shifting the atrial septum to the right attractive [1, 3].

Whight and associates [5] suggested that adequate left atrial enlargement may result from incorporation of the common pulmonary venous sinus into the LA by the repair. Nevertheless, a diminutive LA may complicate the results of TAPVC repair, especially when performed in the infant's first months of life [1, 4, 5].

Furthermore, there appears to be a 6% to 14% chance of severe anastomotic stricture formation when operation is performed in the first year of life, whereas in most patients subsequent further enlargement occurs with growth if the initial anastomosis is large enough [3]. Our experience allows us the following conclusions: (1) the double-patch technique is easy to reproduce, (2) it allows adequate left atrial enlargement at any age and body weight, and (3) it provides reliable early and late results.

We thank Giorgio Donini for skillful artwork.

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Transvenous Pacing in Infants and Children With Congenital Heart Disease

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A technique for transvenous pacemaker implantation in children with complex heart disease is described. The use of small positive-fixation leads, introducers, retained guidewires, and atrial lead loops to allow for growth all have an important role in management of this often challenging problem.

(Ann Thorac Surg 1990;49:495–6)

Postoperative heart block is a recognized complication of repair of congenital heart disease, resulting in high mortality unless permanent pacing is established [1]. Although epicardial pacing is often useful in this setting, transvenous pacing is a desirable alternative either as a primary means of therapy or for replacement of failed epicardial leads [2]. Recent improvements both in technique and in design of leads, introducers, and pacemaker generators allow transvenous pacing to be established consistently despite congenital malformation of the heart and great vessels.

Material and Methods

General anesthesia, maintenance of heart rate with drugs or temporary pacing, excellent fluoroscopy, and electrocardiographic monitoring are minimum requirements. A cephalic or other small venous branch is exposed through a 3- to 4-cm incision beneath the left clavicle. A flexible guidewire is introduced through a small venotomy and passed centrally under fluoroscopic control. A 7F strip-away percutaneous catheter introducer (model 405108, Daig Corp, Minnetonka, MN) is passed over the wire and used to introduce a unipolar, positive fixation, screw-in permanent pacing electrode (model 435-02, Intermedics, Inc, Freeport, TX) (Fig 1). If dual-chamber pacing is required, the guidewire is reintroduced through the introducer before the introducer is removed. A hemostatic pursestring suture is also placed around the vein remnant or pectoralis muscle before the introducer is removed. The guidewire is clamped to the drapes to prevent its migration while the first lead is introduced into the right ventricle by standard techniques. A generous loop of extra lead is advanced into the right atrium after the stylet is removed from the lead to allow for patient growth (Fig 2). Adequacy of R-wave amplitude and pacing thresholds is confirmed.

If an atrial lead is also needed, the ventricular lead is marked with a free tie at the generator end and also tied into position, using the securing sleeve at the entry site. The stylet is reintroduced into only the subclavian portion of the ventricular lead to stiffen it against migration during introduction of the atrial lead, and the ventricular lead is held securely at the venous entry site by an assistant, also to prevent migration. A second 7F strip-away introducer is passed over the guidewire previously left in the vein and the second lead is introduced, tested, and positioned, leaving redundant lead to allow for growth. A hemostatic subcutaneous pocket is fashioned, and the leads are attached to a small unipolar generator, with function confirmed by electrocardiographic analysis and lead position by repeat fluoroscopy before the patient is undraped and awakened.

Comment

The use of guidewires, strip-away introducers, and positive fixation leads in transvenous pacing has been well described [3–5]. These methods are particularly useful for the specific problem of transvenous pacing in congenital heart disease, for which subclavian puncture is potentially hazardous. Anatomical problems in these patients include persistent left superior vena cava (see Fig 2) as well as venous thrombosis related to previous operations or use of central lines for monitoring or nutrition. The retained guidewire technique [6] can also be used with direct subclavian puncture, but use of a small peripheral vein to introduce the guidewire can avoid the hazards of subclavian puncture [5].

Unipolar leads and generators require additional care to limit oversensing and pectoralis or diaphragmatic pacing, but unipolar construction allows use of a lead with a very small cross-section (see Fig 1). Small lead size permits use of small introducers, increased lead flexibility, and less venous obstruction. The positive-fixation feature permits unusual intraventricular locations (Fig 3) and redundant lead loops (see Figs 2, 3). The 435-02 lead design includes permanent exposure of the fixation coil. This requires some experience to avoid snagging on chordae tendineae and other obstacles on the path to the right ventricle. Although leads with retractable fixation coils are available, this feature results in a larger lead tip and heavier lead shaft. Bipolar positive-fixation leads are relatively stiff and more cumbersome to use in infants and small children. We have not used these methods in newborn or premature infants in whom access through the external jugular vein and removal of the stylet during lead manipulation are likely to be useful modifications. The smallest

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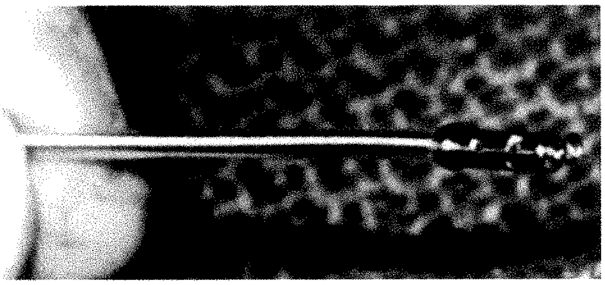

Fig 1. Positive-fixation, screw-in lead has polyurethane insulation, small cross-section, and a permanently extended fixation coil. Counterclockwise rotation minimizes "hang-ups" during insertion.

pacemaker generators currently available are satisfactory for subcutaneous sites, except in small infants.

Redundant right atrial lead loops should allow for 5 to 10 years of growth in these patients (Gheissari A and Spotnitz HM, unpublished data). The techniques described have been used in 2 infants (aged 9 and 12 months) and 13 children (aged 3, 3, 5, 5, 5, 6, 6, 7, 7, 8, 9, 9, and 10 years) at the Columbia-Presbyterian Medical Center since October 1985 with no complications or need for reoperation. In adults, 342 endocardial screw-in leads have been used, with no ventricular lead displacement. The atrial lead displacement rate in adults has been 3%. No perfect method of long-term pacing has been demonstrated, and both exit block and lead displacement can be anticipated in the younger population as our experience increases. It is hoped that this description will improve the results of transvenous pacing in this often challenging group of patients.

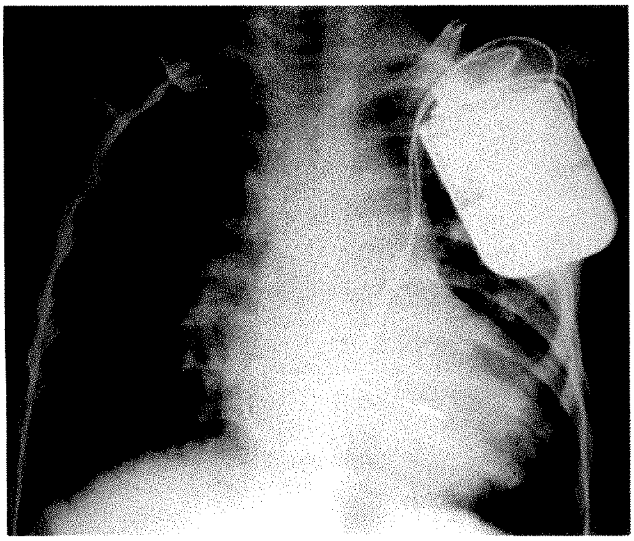

Fig 2. Transvenous dual-chamber demand pacemaker inserted in October 1985 in a 3-year-old child for complete heart block after mitral valve replacement. The leads enter the heart through the left superior vena cava and the coronary sinus. Lead loops provide extra length to allow for growth. A longer loop for the atrial lead would be preferable but was prevented by the location of entry into the right atrium.

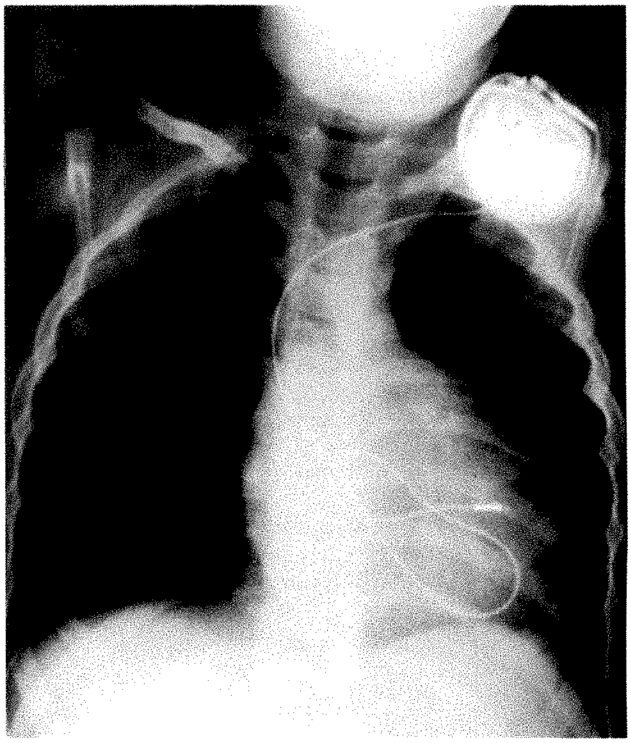

Fig 3. Ventricular inhibited pacemaker inserted in a 6-year-old child with corrected transposition for sick sinus syndrome after closure of an atrial septal defect. The lead is placed high in the outflow tract of the right ventricle to prevent diaphragmatic pacing, which was observed from locations closer to the apex. A generous lead loop allows for growth. Lead loops and outflow tract pacing are likely to result in lead displacement unless positive fixation leads are used.

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Werner Forssmann and Catheterization of the Heart, 1929

John A. Meyer, MD

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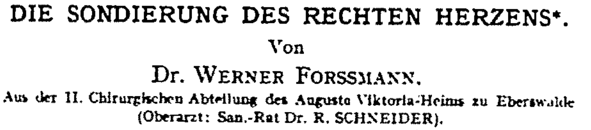
Invasive study of cardiac anatomy and function traces its origin to the work of a 25-year-old surgical trainee in a provincial German town in the pre-Depression years of 1929 and 1930. Only 1 year out of medical school and undeterred by the medical profession's fear of tampering with the heart, Dr Werner Forssmann explored methods for a more direct access to the cardiac chambers, finding it necessary to make the observations on himself. Later he was able to show that the right-sided cardiac chambers could be visualized radiographically after injection of iodinated contrast materials through a catheter into the right atrium, and again he tried the method on himself.

(Ann Thorac Surg 1990;49:497–9)



DIE SONDIERUNG DES RECHTEN HERZENS*.

Von

Dr. WERNER FORSSMANN.

Aus der II. Chirurgischen Abteilung des Augusta Viktoria-Heims zu Eberswalde
(Oberarzt: San.-Rat Dr. R. SCHNEIDER).

Fig 1. Title and byline of Dr Werner Forssmann's landmark first paper, 1929. Translation: Probing of the right heart. From the 2nd Surgical Unit of the Augusta Victoria Home in Eberswalde. (Chief Physician: Health Councillor Dr R. Schneider.)

Doctor Werner Forssmann, aged 24 years and just awarded his medical degree from the University of Berlin, began postgraduate training in surgery at Eberswalde in 1928. Eberswalde was a provincial town some 45 km northeast of Berlin, but its hospital, the Augusta Victoria Home, was an affiliate of Professor Ferdinand Sauerbruch's program. One year after the start of his training, in 1929, Forssmann began a study of the feasibility of more direct access to the heart.

> In many emergency situations, patients may be threatened by stoppage of the heart's activity, as in acute collapse due to heart disease, or anesthetic accidents or poisonings, and will require immediate treatment on the spot. In such cases, the sole resort often is a trial of intracardiac injection, by which life may occasionally be restored. Nevertheless intracardiac injection will always remain a dangerous undertaking in many instances, since puncture of the wall of the heart may injure the coronary vessels or their branches so that bleeding into the pericardium may result in fatal cardiac tamponade. Also chest puncture may result in fatal pneumothorax. Such risks are likely to make a physician leave intracardiac injection to the last moment, so that he may lose the most valuable time for direct delivery of medications to the heart. These considerations encouraged me to seek for a new method by which access could be gained to the heart without danger, and I sought to begin *exploration of the right heart by way of the venous system* (italics in the original) [1].

What tools might have been available to him, in what seems to us a comparatively low-technology era? Ureteral catheters similar to those of today were in regular use, and both radiographic apparatus and darkroom fluoroscopy equipment were installed in most hospitals. The autopsy suite was available for investigative purposes. To begin, Forssmann enlisted the help of an anonymous colleague.

> After successful tests upon a cadaver, I undertook the first study on a living person, in the form of an experiment upon myself. First, I submitted to a preliminary test of the method; for this, a colleague had kindly placed himself at my disposal, to puncture the antecubital vein with a large needle. I instructed him then, as we had done on the cadaver, to pass a well-oiled ureteral catheter of size 4 Charrières* through the cannula into the vein. The catheter could be introduced with ease to a distance of 35 cm. At this point my colleague believed that further passage would be too dangerous and that we must terminate the experiment, a decision with which I was obliged to agree.
>
> One week later I undertook a further experiment by myself. I used a local anesthetic, and since it proved too difficult to do a venipuncture upon myself with a large needle, I did a venesection at my left elbow and passed the catheter without any resistance to its full length, 65 cm. This distance appeared to me, after having measured on the body surface, to correspond to the distance from the left elbow to the heart. During passage of the catheter I was aware only of a slight feeling of warmth from its sliding along the vein wall, similar to the feeling one notices during intravenous injection of calcium chloride. During repeated passages the catheter often encountered a partial obstruction at the upper margin of the subclavian vein; at these times I experienced a particularly warm sensation behind the clavicle, at the base of the neck; and at the same time because of stimulation of the vagus trunk, a slight irritating cough.

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Excerpts from Forssmann's studies are in translation by Dr Meyer.

* The same designation as our 4F, approximately 1.3 mm in diameter.

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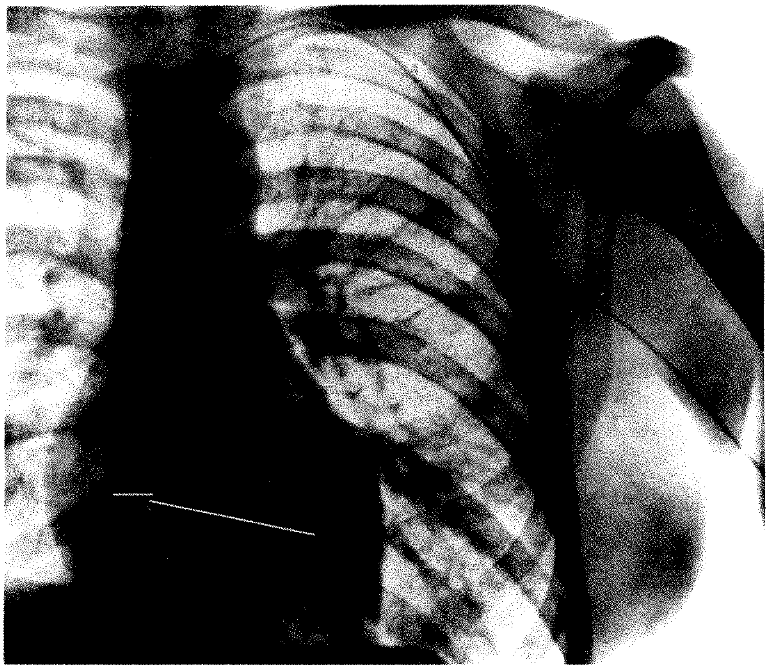

Fig 2. Original caption translated as "The catheter passes inward from the left cephalic vein (sic), turning downward as far as the right atrium [1]." Position of the catheter tip is marked by the arrow. *(Reprinted from [1] by permission of Springer-Verlag, Munich, FRG).*

> I recorded the positions of the catheter by obtaining x-ray films, and I was able to observe the advancing catheter clearly on the fluoroscopic screen, by means of a mirror held for me by the Sister.
>
> . . . Figure 2 is a film of the second observation: the catheter passes directly inward from the left arm, under the clavicle at the chest wall, and makes a downward bend at the place of junction with the jugular vein, lying near the margin of the great-vessel shadow and the shadow of the spine, and reaching as far as the right atrium. On another passage, the catheter did not reach any further than this.
>
> I watched carefully for any other effects, or signs of irritation of the cardiac mechanism, but could not identify any. In our institution there is a considerable distance between the operating rooms and the x-ray unit. To go from one to the other I had to climb staircases on foot and return, while the probe was lying within my heart, but I was not aware of any unpleasantness. Passage and removal of the catheter were entirely painless, accompanied only by the above-mentioned sensations. Later on I could find no sequelae to the procedure, except for a slight inflammation at the site of venesection, which clearly was a result of inadequate asepsis during the self-performed operation . . .
>
> (Closing, page 2087.) In conclusion I should point out that this method . . . has opened the prospect of many possible metabolic researches and studies of the function of the heart, some of which I have already begun [1].

The first study that he undertook was the injection of radiographic contrast materials through a right atrial catheter with x-ray filming, first in the hearts of dead animals and then in those of living ones [2]. The rapid film-cassette changer had not yet been invented, so timing of a single film with the contrast injection was difficult at first. Good pictures of the right-sided chambers and the pulmonary artery could be obtained, however, and Forssmann again used himself as an experimental subject. On two separate occasions he injected the contrast material through catheters (No. 8 Charrières in these experiments) into his own right atrium, but on these occasions the x-ray exposures were mistimed and satisfactory films were not obtained. During the injections, he described a transient sensation of dizziness, and moments afterward, a sensation of warmth in the mouth, but no other adverse effects. He presented his findings before the Medical Society of Eberswalde on November 29, 1930, and published them in another journal in the following year [2].

> **Summary** (p. 492):
> 1. Filling of the cadaverous heart with Röntgen-contrast materials can produce beautiful pictures, but does not demonstrate the corresponding functional relationships.
> 2. With the help of a cardiac catheter, it is possible to introduce contrast materials into the living right heart.
> 3. Rapid injection of sodium iodide in a 25 percent solution, and Uroselectan in 50 percent solution, were well tolerated by experimental animals and resulted in good (x-ray) pictures.
> 4. During two experimental trials on the same person, with rapid injections of sodium iodide and Uroselectan through a catheter into the right atrium, no unpleasantness or adverse reactions were observed. Satisfactory contrast photographs were not obtained, because of faulty technique on our part [2].

Epilogue

Forssmann gave up pursuing these studies, possibly because of opposition from his colleagues and superiors. Subsequently he took additional postgraduate training in urology at Berlin and Mainz and began his practice in Dresden. He served as a medical officer in the German Army during World War II and was taken prisoner on the Western Front. Released at the end of 1945, he returned to urological practice together with his wife, who was also a physician with similar training.

A decade after his landmark report, catheterization of the heart was taken up by André Cournand and Dickinson W. Richards of Columbia University and developed into a systematic method for diagnostic study of the cardiac chambers. Dr Cournand (1895 to 1988), though not a surgeon, was for many years a member and senior member of the American Association for Thoracic Surgery. Forssmann, Cournand, and Richards shared the Nobel Prize for Medicine or Physiology in 1956. Forssmann died in 1978 at the age of 74.

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REVIEW OF RECENT BOOKS

Cardiac Arrhythmias, 3rd ed
By Davis H. Bennett
Butterworths (John Wright), 1989
206 pp, illustrated, $49.95

Reviewed by Richard M. Peters, MD

This paperback volume reviews the clinical and electrocardiographic findings and treatment of patients with arrhythmias. The book is well organized with good electrocardiographic illustrations and summary of the findings on each type of arrhythmia. The book is designed for those who are not at the level of electrophysiologists. It appears to be a good book for house officers and an advanced book for medical students. It will allow one to look up the arrhythmias that are associated with different conditions as, for example, myocardial infarction and atrioventricular blocks. Not only the electrocardiographic manifestations but also the suggested treatment modalities are given.

San Diego, California

Congenital Bronchoesophageal Fistula

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Congenital bronchoesophageal fistula is a rare anomaly that normally appears in adult life. Because of a recent case, we reviewed the literature on this lesion. There have been several reviews in the past but none has included all cases. The largest review included only two thirds of the cases (1966). Including our case, the number of reported cases is 100.

(Ann Thorac Surg 1990;49:500–5)

Congenital bronchoesophageal fistula (BEF) is a rare anomaly that usually appears in adult life. The clinical course is insidious, and diagnosis is made by barium esophagram. Treatment is surgical with excellent results. Only 99 cases have been reported in the world literature. A recent representative case from our institution is presented along with a review of the literature.

Case Presentation

An 11-year-old girl was born with a left diaphragmatic hernia that was repaired shortly after birth. At 2 months of age, the child underwent an exploratory laparotomy with small bowel resection for volvulus. She did well until 5 months before admission when coughing and choking, first with liquid and then with solid intake, developed. The patient never had respiratory distress or pulmonary infections. After the symptoms became progressively worse, she was evaluated.

Chest roentgenogram was normal. A cinefluoroscopic esophagram revealed BEF with communication between the middle third of the esophagus and the bronchus intermedius (Fig 1). Remaining admission laboratory work was normal.

She underwent a right thoractomy with division of the fistulous tract. The dissection was simple, and there was no evidence of past or present inflammation around the fistulous tract, bronchus, or esophagus (Figs 2, 3). There were no adherent lymph nodes. Postoperatively, the patient's symptoms completely resolved. She was discharged on postoperative day 5. On follow-up 12 months postoperatively, she was still asymptomatic.

Comment

Bronchoesophageal fistula may be congenital, traumatic, inflammatory, or neoplastic. Congenital BEFs are very rare, with only 99 cases previously reported. The largest review had only 68 cases [1]. Several reviews of the literature have had overlapping reported cases [1–4]. This current review includes all cases from 1916 [5] to the present (Table 1).

A review of the literature shows that BEFs occur in equal frequency in male (53%) and female patients (47%). The youngest patient was a 9-day-old boy who underwent division of the fistulous tract to the right lower lobe [9]. The oldest was an 83-year-old man who had division of the fistulous tract to the right main bronchus [7]. Twenty-four percent of the cases occurred in the pediatric age group (17 years of age or younger).

The most common location of the fistula was between the middle third of the esophagus and the right lower lobe (41 patients); other locations included the left lower lobe (21), right main bronchus (18), bronchus intermedius (10),

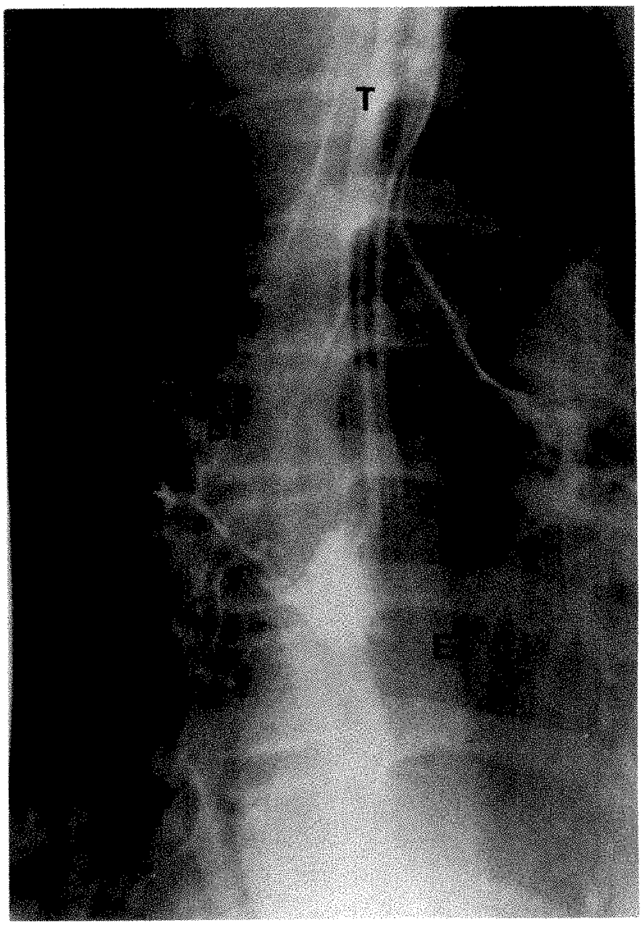

Fig 1. Cinefluoroscopic esophagram showing bronchoesophageal fistula between the middle third of the esophagus and the bronchus intermedius. (BI = bronchus intermedius; E = esophagus; LM = left main bronchus; T = trachea.)

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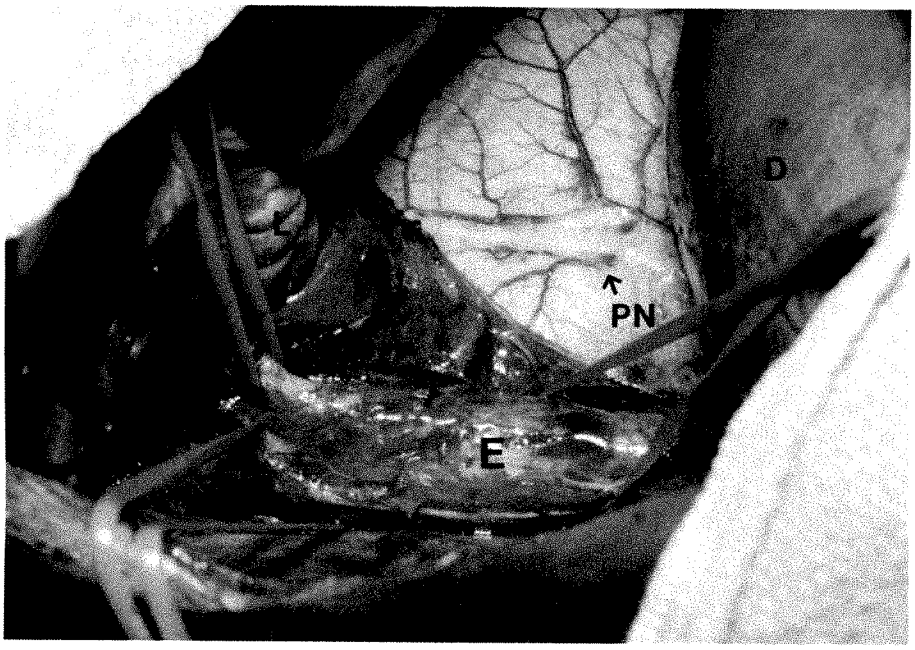

Fig 2. Intraoperative photograph from surgical exploration showing bronchoesophageal fistula. (D = diaphragm; E = esophagus; FT = fistula tract; L = lung; PN = phrenic nerve.)

left main bronchus (6), right middle lobe (2), and right upper lobe (2). There were no fistulas to the left upper lobe (Fig 4). There were three fistulas to sequestered lobes and five fistulas to a cyst (three to the right lower lobe and two to the left lower lobe).

The embryological explanation of the origin of BEF was given by Smith [11]. The tracheal band appears on the ventral aspect of the primitive foregut at the 3-mm stage. At the 5-mm stage there is rapid elongation of the trachea, which then separates from the esophagus. A persistent attachment between the tracheobronchial tree and the esophagus will result from the incoordination of these two processes. The eventual site of the fistula in the broncheal tree will depend on the degree of tracheoesophageal separation that occurs before caudal elongation of the trachea. Therefore, if rapid growth occurs early, the fistula will be low in the bronchial tree.

The congenital nature of the fistula may be assumed if there is no evidence of past or present inflammation around the fistulous tract or esophagus, if there are no adherent lymph nodes, and if there is a mucosa and muscularis mucosa histologically [7]. The absence of inflammation makes dissection of the fistula simple at operation and virtually excludes a previous inflammatory cause for the lesion [2].

Congenital BEFs were classified by Braimbridge and

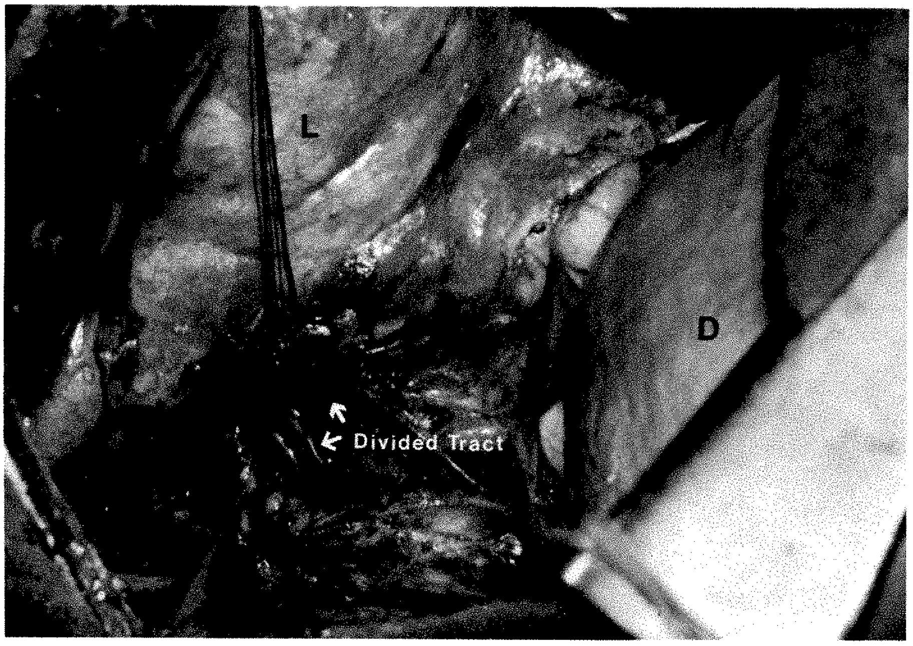

Fig 3. After division of fistulous tract. (D = diaphragm; L = lung.)

Table 1. Bronchoesophaageal Fistula (1916–1988)

Author	Year	Age (yr)	Sex	Bronchial Communication
Heiderich [5]	1916	NM	M	Right BEF: main bronchus
Lantuejoul [1]	1920	6	M	Left main bronchus
Clerf [6]	1933	23	F	Left BEF: left lower lobe
Camplani [1]	1936	42	F	Right BEF: branch of right lower lobe bronchus
Moersch [1]	1937	52	M	Left BEF: left lower lobe bronchus
Tobias [1]	1937	35	M	Right BEF: base of main bronchus
Golimari [1]	1939	20	M	Left BEF: "left inferior bronchus"
Berman [1]	1943	23 mo	M	Right bronchial tree
Berglund [1]	1947	62	M	Right BEF: lower lobe segmental bronchus
Brunner [7]	1948	42	M	Right BEF: main bronchus?
	1948	44	F	Right BEF: middle lobe bronchus
Testa [1]	1948	45	M	Right BEF: main bronchus
Morton [1]	1950	26	M	Right BEF: lower lobe segmental bronchus
Jenkinson [1]	1951	61	M	Right BEF: main bronchus
Boquien [1]	1952	16	F	Right BEF: lower lobe secondary bronchus
Dor [1]	1952	29	F	Right BEF: lower lobe bronchus
Finke [1]	1952	17	F	Right BEF: lower lobe segmental bronchus
Berman [1]	1953	40	F	Left BEF: lower lobe segmental bronchus
Kaiser [1]	1953	9 wk	M	Left main bronchus
Levine [1]	1953	42	M	Right BEF: lower lobe segmental bronchus
Linder [1]	1953	37	F	Right BEF: main bronchus
Thomas [1]	1953	13	F	Right main bronchus
	1953	14	F	Main bronchus, left?
Abrams [1]	1954	38	M	Right BEF: lower lobe segmental bronchus
Mathey and Lemoine [4]	1954	16	F	Right lower lobe
Mullard [1]	1954	54	F	Right BEF: right dorsal lobe bronchus
	1954	54	M	Left BEF: main bronchus
Schoenbauer [1]	1954	39	M	Right BEF: lower lobe segmental bronchus
	1954	51	F	Right BEF: lower lobe bronchus and cyst
Roger [1]	1955	56	F	Right BEF: base of main bronchus
Bjorklund [1]	1956	45	M	Left BEF: lower lobe terminal bronchus
Davidson [1]	1956	16	M	Left BEF: lower lobe terminal bronchus and cyst
Duprez [1]	1956	18	F	Right BEF: middle lobe bronchus
Mugrditchian [1]	1956	46	F	Right BEF: lower lobe segmental bronchus
Polak [1]	1956	28	F	Left BEF: lower lobe segmental bronchus
St. Raymond [1]	1956	13	M	Left bronchial fistula to accessory lung lobe
Wassner [1]	1956	5	M	Right main bronchus
	1956	49	M	Right BEF: lower lobe segmental bronchus
Fornara [1]	1957	5 mo	M	Right "superior bronchus"
Fromme [1]	1957	47	F	Left BEF: lower lobe "fine bronchus"
Brunner [1]	1958	33	M	Right BEF: bronchus intermedius
Polak et al [2]	1958	27	M	Left lower lobe
Ware [1]	1958	39	M	Right BEF: lower lobe segmental bronchus
Billimoria [1]	1959	14	M	Right lower lobe bronchus
	1959	12	M	Right main bronchus
	1959	4 mo	F	Right intermediate bronchus
	1959	4	F	Right lower lobe bronchus
	1959	12	F	Left lower lobe bronchus
	1959	35	F	Right BEF: lower lobe bronchus
Das [1]	1959	31	M	Left BEF: lobe segmental bronchus
Demong et al [8]	1959	30	M	Right BEF: intermediate bronchus
Guillon [1]	1959	41	M	Right BEF: lower lobe segmental bronchus

Table 1. Continued

Author	Year	Age (yr)	Sex	Bronchial Communication
Svetozarov [1]	1959	52	F	Right BEF: lower lobe bronchus
Donatelli [1]	1960	30	M	Right BEF: right lower lobe segmental bronchus
Lansden [1]	1960	60	M	Right BEF: main bronchus
Lhotak [1]	1960	18 mo	F	Right bronchial tree
Brunner [7]	1961	33	F	Right lower lobe apex
	1961	83	M	Right main bronchus
	1961	83	F	Right main bronchus
	1961	55	M	Left BEF: lower lobe bronchus
Dorfman [1]	1961	31	M	Right BEF: lower lobe segmental bronchus
Hewitson [2]	1961	26	F	Right lower lobe
Hewitson [1]	1961	19	F	Left BEF: lower lobe segmental bronchus
Miller [4]	1961	75	F	Left lower lobe
Halasz [1]	1962	30	F	Right BEF: segmental bronchus
Thomson and Aquinto [9]	1962	9 days	M	Fistula served as right lower lobe bronchus
Frater [1]	1964	39	M	Right BEF: bronchus intermedius
Tanaka [1]	1964	25	M	Left BEF: main bronchus
Tormo [1]	1964	6 mo	M	Right main bronchus
Braimbridge and Keith [2]	1965	42	F	Right BEF: lower lobe bronchus
	1965	19	M	Right BEF: lower lobe segmental bronchus and cyst
	1965	34	F	Left BEF: lower lobe segmental bronchus and cyst
Wayson [1]	1965	infant	NM	Right main bronchus
Ashley and Evans [3]	1966	45	M	Left sequestered lung
Blackburn and Raymond [1]	1966	60	F	Right BEF: lower lobe segmental bronchus
	1966	51	F	Right BEF: lower lobe segmental bronchus
Harris et al [3]	1967	63	M	Bronchus intermedius
Sacks et al [3]	1967	39	F	Right upper lobe subsegmental bronchus
LeRoux and Williams [3]	1968	54	F	Bronchus intermedius
	1968	23	F	Bronchus intermedius
	1968	44	M	Right lower lobe bronchus
Mascarella and Wylie [3]	1968	18	F	Sequestrated lung
Kinley and Lang [3]	1969	59	F	Posterior basal segment right lower lobe
Bertelsen [4]	1970	48	M	Right main bronchus
Nelson and Benfield [10]	1970	22	F	Bronchus intermedius
Paulin et al [3]	1970	66	M	Superior segment right lower lobe
Smith [11]	1970	31	M	Postbasal segment right lower lobe
Hill [3]	1972	29	M	Postbasal segment right lower lobe
Vaages [3]	1973	56	F	Cyst postbasal segment right lower lobe
Bekoe et al [3]	1974	60	F	Right lower lobe bronchus
Darakaju et al [3]	1974	20	F	Apical segment right upper lobe
	1974	11	M	Postbasal segment right lower lobe
	1974	10	M	Postbasal segment right lower lobe
Becker et al [3]	1976	62	F	Left main bronchus
Salepcioglu et al [12]	1977	37	F	Right lower lobe bronchus
Chu and Mullen [13]	1978	58	M	Bronchus intermedius
Osinowo et al [3]	1983	46	M	Subsegmental bronchus of apical segment left lower lobe bronchial tree
Kameya et al [14]	1984	43	M	Right lower lobe bronchus (medial basal segment)
Smith et al [4]	1987	68	M	Left main bronchus
Risher [present report]	1990	11	F	Bronchus intermedius

BEF = bronchoesophageal fistula; F = female; M = male; NM = not mentioned.

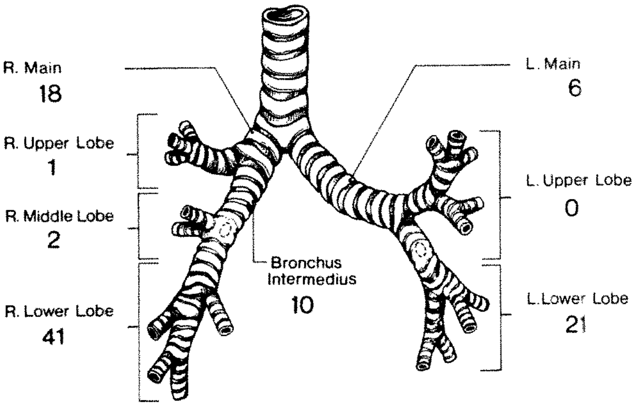

Fig 4. Distribution of bronchoesophageal fistula by location of bronchial portion of fistula.

Keith [2] into four types (Fig 5). Type I is associated with a wide-necked congenital diverticulum of the esophagus. Stasis may occur in the dependent tip, which becomes inflamed and perforates into the lung. Type II is the simplest and most common. A short tract runs directly from the esophagus to the lobar or segmental bronchus. The patient whose case is presented in this report had a type II BEF. Type III consists of a fistulous tract connecting the esophagus to a cyst in the lobe, which in time communicates with the bronchus (only 5 cases). In Type IV the fistula runs into a sequestered segment, which is recognized by the presence of a systemic arterial supply from the aorta. The sequestration connects with the esophagus by one or more fistulous tracts (only 3 cases).

Symptoms occasionally begin in childhood but rarely at birth. The cause of the delay has been attributed to the presence of a membrane that subsequently ruptures [15], to the proximal fold of esophageal mucosa initially overlapping the orifice but subsequently becoming less mobile [16], and to the fact that the fistulous tract runs upward and may close during swallowing, as was seen in our patient (Fig 6) [8].

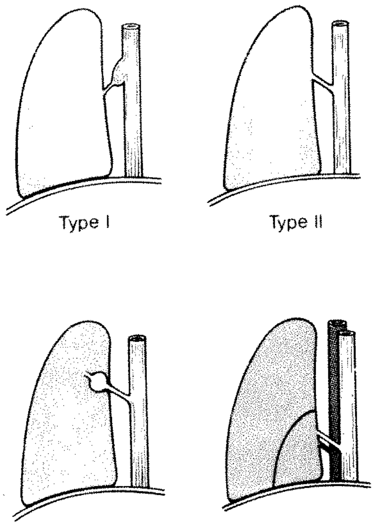

Fig 5. Classification of congenital bronchoesophageal fistula: type I, wide neck diverticulum with inflammatory fistula at tip; type II, simple fistula; type III, fistula with cyst; type IV, fistula with sequestration segment. (Adapted from [2] by permission of the British Medical Association.)

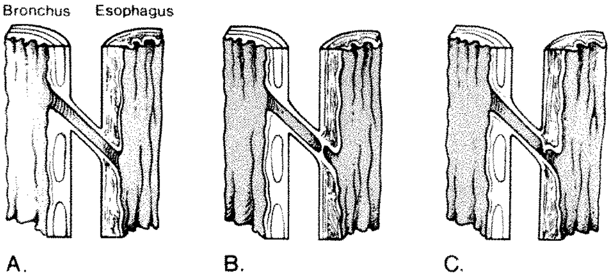

Fig 6. Reasons for delay in onset of symptoms: (A) fistula runs upward; (B) complete membrane; (C) fold of mucous membrane. (Adapted from [2] by permission of the British Medical Association.)

The duration of symptoms may vary from 6 months to 50 years before treatment. Symptoms may not begin until adult life and are often intermittent. They are usually due to chronic bronchopulmonary suppuration, cough (almost universal), pneumonia, and hemoptysis. The presence of food in the sputum or choking on swallowing liquids may lead to a diagnosis of BEF. More uncommon symptoms include dysphagia, epigastric discomfort, and reflux caused by the stomach filling with air on expiration.

The fistula does not usually give rise to physical signs. The diagnosis is usually made by barium esophagram when the opaque medium is seen to pass into the lung, outlining the fistulous tract. Bronchoscopy and esophagoscopy will sometimes demonstrate the orifices of the fistula, which are usually small and only recognizable when the exact sites are known [2]. In spite of extensive investigation, the diagnosis may be made only at operation.

Treatment consists of closure of the fistula and excision of any permanently damaged lung segments. Cure has been reported after obliteration of the esophageal end of the fistula with silver nitrate, but this is an unreliable technique reserved for those patients who would not tolerate operation [6]. There was no operative mortality in the review of cases of BEF.

Conclusion

Ninety-nine cases of BEF (excluding the 1 in this report) are reported in the literature. Bronchoesophageal fistula occurs in equal frequency in male and female patients; 76% of the cases occur in adults. Onset of symptoms is insidious, and diagnosis is confirmed by barium esophagram. Treatment involves closure of the fistula and resection of any premanently damaged lung segments.

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Mediastinitis After Cardiac Operations

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Historical

1. Shumaker HB, Mandelbaum I. Continuous antibiotic irrigation in the treatment of infection. Arch Surg 1963;86:384–7.
   This is the initial report of mediastinal irrigation after debridement and closure of wound.
2. Bryant LR, Spencer FC, Trinkle JK. Treatment of median sternotomy infection by mediastinal irrigation with an antibiotic solution. Ann Surg 1969;169:914–20.
   This report describes a modification of irrigation technique; it reports an 80% survival for postoperative mediastinitis.
3. Lee AB, Schimert G, Shatkin S, Seigel JH. Total excision of the sternum and thoracic pedicle transposition of the greater omentum; useful stratagems in managing severe mediastinal infection following open heart surgery. Surgery 1976;80:433–6.
   This article reports successful treatment of 2 patients with radical debridement and omental transfer with skin grafts.
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   This is the initial report of use of muscle flaps in reconstruction of infected sternotomy wound.
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   This is a classic study of blood supply to sternum demonstrating periosteal arcade and blood supply from mammary perforators.

Incidence and Diagnosis

6. Ottino G, DePaulis R, Pansini S, et al. Major sternal wound infection after open-heart surgery: a multivariate analysis of risk factors in 2,579 consecutive operative procedures. Ann Thorac Surg 1987;44:173–9.
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   In 6,504 patients there was a 1.1% overall wound complication rate, and the use of bilateral mammary artery grafts in diabetic patients raised the risk of wound infection 3.9-fold.
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    This is a review of postoperative mediastinitis before widespread use of muscle flap closure.

Debridement and Closed Irrigation

11. Grossi EA, Culliford AT, Kreiger KH, et al. A survey of 77 major infectious complications of median sternotomy: a review of 7949 consecutive operative procedures. Ann Thorac Surg 1985;40:214–22.
    In 77 patients with sternal wound infection there was a 76% success rate with closed irrigation technique.
12. Cheung E, Craver J, Jones E, Murphy D, Hatcher C Jr, Guyton R. Mediastinitis after cardiac valve operations. J Thorac Cardiovasc Surg 1985;90:517–22.
    Thirty-six patients from 2,491 procedures (1.4%) over 10 years were treated for sternal wound infection with a 36% mortality.
13. Kopel M, Riemersma L, Finlayson D, et al. Gentamicin solution for mediastinal irrigation: systemic absorption, bactericidal activity, and toxicity. Ann Thorac Surg 1989;48:228–31.
    This is a study of pharmacokinetics of gentamicin in mediastinal irrigation solutions.
14. Campistol J, Cipriano A, Nogue S, Bertrain A. Acute renal failure in patient treated by continuous povidone-iodine mediastinal irrigation. J Cardiovasc Surg 1988;29:410–2.
    Renal insufficiency developed in a patient with irrigation and reversed with withdrawal of Betadine.

Soft Tissue Closure

15. Nahai F, Rand R, Hester R, Bostwick J, Jurkiewicz M. Primary treatment of the infected sternotomy wound with muscle flaps: a review of 211 consecutive cases. Plast Reconstr Surg 1989;84:434–41.
    In this, the largest series of patients treated with muscle flaps, 65% were debrided and closed with flaps at the same operation. There was a 5.3% mortality and 17.5% persistent infection rate.
16. Heath B, Bagnato J. Poststernotomy mediastinitis treated by omental transfer without postoperative irrigation or drainage. J Thorac Cardiovasc Surg 1987;94:355–60.
    Eight patients were treated with debridement and omental transfer in a single operative procedure with a mortality of 12.5% and a 27-day average hospital stay.
17. Scully H, Leclerc Y, Martin R, et al. Comparison between antibiotic irrigation and mobilization of pectoral muscle flaps in treatment of deep sternal infections. J Thorac Cardiovasc Surg 1985;90:523–31.
    Forty-one patients were treated with muscle flaps over 9 years and compared with historical controls. Comparable functional results between the two groups were shown.
18. Majure J, Albin R, O'Donnell R, Arganese T. Reconstruction of the infected median sternotomy wound. Ann Thorac Surg 1986;42:9–12.
    Eighteen patients over 6 years were treated with muscle flap closure.

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19. Pairolero PC, Arnold PG. Management of infected median sternotomy wounds. Ann Thorac Surg 1986;42:1–2.
This is an editorial on various techniques and applicability for therapy of sternal wounds.

Recurrent Infections

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This report stresses technique for dealing with chronic chondritis.

21. Pairolero PC, Arnold PG. Management of recalcitrant median sternotomy wounds. J Thorac Cardiovasc Surg 1984;88:357–64.
This article describes a combined approach (thoracic and plastic surgery) to long-standing sternal wounds in 38 patients.

Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1992 may begin the recertification process in 1990. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1990. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

CORRESPONDENCE

Mitral Valve Annuloplasty

To the Editor:

The recent report by David and associates [1] on mitral valve annuloplasty deserves particular attention because a superficial reading may lead to the conclusion that a narrowing annuloplasty (flexible ring) is superior to a remodeling annuloplasty (semirigid ring) contrary to clinical findings published in the past 10 years by a growing number of surgeons.

The recovery of normal ventricular function after mitral valve reconstruction has been demonstrated for periods of up to 17 years [2]. Using sophisticated techniques of investigation, namely, Doppler echocardiography and radionuclide angiography, David and associates have tried to determine whether a difference exists between flexible and semirigid rings in the timing of this recovery.

There is little to say with regard to the quality of this study and the statistical analysis used, but the interpretation of the results is open to controversy. In addition to ring flexibility and rigidity, numerous factors may play a role in ventricular function after mitral valve surgery: (1) degenerative valvular diseases, the etiologic group selected for this study, actually comprises at least two different diseases: Barlow's disease and fibroelastic deficiency, which behave quite differently after repair; (2) the complexity of the repair varies with each individual patient; (3) the quality of the myocardial protection also varies because it depends not only on the technique of cardioplegia itself but also on numerous patient-related or heart-related factors; and (4) important also are the different drugs taken by the patients before and after the operation. So many factors could not be taken into consideration in a study that compares one group of 11 patients with rigid rings to another group of 14 patients with flexible rings. This is reflected by the large standard deviations of up to 50% of some data. My colleagues and I noted that the standard deviations were much greater in the rigid-ring group than in the flexible-ring group: 32% versus 16% for the end-diastolic volume index and 50% versus 30% for the end-systolic volume index. The fact that the rigid-ring group was more heterogenous than the flexible-ring group suggests that patients with less favorable lesions were treated, consciously or not, by rigid-ring annuloplasty. We also noticed that the left ventricular function study was performed between 2 and 3 months after the operation, a period of rapid changes in the recovery of the left ventricle. Because 88% (22/25) of the patients were in New York Heart Association functional class III or IV, we can assume that the patients studied in the third month had better left ventricular function than those who were studied in the second month. Did both groups have the same average postoperative period, and did they have the same medications when the left ventricular study was done?

We continue to favor the remodeling annuloplasty concept because it provides a larger orifice area, a reduced incidence of thromboembolism, and a more durable repair. When weighed against those advantages, ring flexibility has a limited importance, all the more so because most of the diseased hearts have lost their annular contractility. However, if indeed there is really a difference in left ventricular function between flexible and rigid rings, the most important point of this report is to demonstrate that this difference is transitory: "6 patients (reinvestigated at 1 year postoperatively) demonstrated a dramatic improvement in left ventricular dimensions, volumes, and systolic function regardless of the type of annuloplasty ring used . . . these results suggest . . . that the left ventricle may have compensatory mechanisms to overcome the problem of a rigid or flexible mitral ring" [1].

Of importance is that this "temporal response" (to use an expression proposed by Schuler for valve replacement) did not preclude the fast clinical recovery of the patients belonging to the rigid-ring group: no postoperative complications were encountered in the rigid-ring group versus two severe complications in the flexible-ring group. We can conclude that the comparative performances of remodeling annuloplasties and narrowing annuloplasties should be based on more durable findings such as mitral valve orifice area, incidence of thromboembolic complications, patient survival, and long-term stability of the repair [2].

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Reply

To the Editor:

Dr Carpentier is the father of modern mitral valve repair and has taught the principles of this operation to many hundreds of cardiac surgeons, including myself. I have to agree with his remark that narrowing annuloplasty is not superior to remodelling annuloplasty. That was not the message of our report [1]. I believe (as he does) that annuloplasty is only part of a mitral valve reconstructive procedure.

Dr Carpentier is correct in stating that Barlow's disease and fibroelastic deficiency of the mitral valve behave differently after repair of mitral valve regurgitation. The main difference as far as postoperative left ventricular function is concerned is the fact that patients with Barlow's disease have an increased incidence of left ventricular outflow tract obstruction after mitral valve repair. Although this problem has been described in patients who had a rigid annuloplasty [2], I have seen similar cases in patients with flexible rings. My colleagues and I had only 1 patient with this problem and he was removed from our study [1].

As far as the complexity of the repair affecting the postoperative left ventricular function, the only factor known to me is that extensive resection of the posterior leaflet with plication of the mitral annulus is associated with postoperative segmental hypokinesis of the basoconstrictors. The portion of the annulus that is plicated probably impairs the stretching and shortening of the adjacent ventricular muscle. By applying one of Dr Carpentier's recent technical innovations, what he refers to as "sliding plasty of the posterior leaflet," we have been able to abolish this problem. I only learned about this problem recently, but it is unlikely that this would explain the differences encountered in systolic function in our patients [1].

As we stated in our article [1], we did not pay excessive attention to myocardial protection, but all patients were operated on with the same care and technique. We used blood cardioplegia in all patients. We cross-clamped the aorta and gave cardioplegia as soon as cardiopulmonary bypass was established. We did not inspect the mitral valve in a beating or fibrillating heart.

Several patients were on afterload-reducing agents before operation, but no patient was on this type of therapy postoperatively. Patients in atrial fibrillation were taking digitalis.

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The number of patients randomized was small, but they were carefully studied without any intraoperative or postoperative bias. The differences in left ventricular function 2 to 3 months after operation were statistically significant. The average intervals between the preoperative and postoperative studies were similar in both groups of patients.

Dr Carpentier brought up an important point in his letter: the temporal response of left ventricular function after mitral valve repair. As we stated in the discussion of our article, our patients were being restudied at 1 year after the operation, and the results indicated that the ventricular function in these patients continues to improve beyond 3 months. At 1 year after operation most patients have remarkably normal ventricular function regardless of the type of ring used during mitral valve repair as long as the preoperative function was not excessively depressed.

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Cryoanalgesia for Postthoracotomy Pain

To the Editor:

We strongly disagree with the editorial on cryoanalgesia [1] accompanying the paper by Müller and associates [2]. Although opposing views should be expressed in an editorial accompanying an original paper, they must be valid, supported by fact, not just impressions.

Dr Katz says that "perhaps the most disturbing portion of the paper by Müller and associates was the incidence of postthoracotomy dysesthesias." This is disturbing, but not as disturbing as the main finding of a well-controlled double-blind trial that there was *no advantage in using cryoanalgesia at all.*

Is cryoanalgesia an effective means of postthoracotomy pain control? As Müller and associates report, initial work on cryoanalgesia did report lower pain scores and decreased analgesic requirements, but these studies used small populations [3] or failed to use an untreated control group [4]. This finding was also reported by Katz and associates [5], but this paper and another [6] subsequently failed to show any improvement in lung function tests compared with controls. Orr and colleagues [7] failed to show any significant improvement in pain on movement and during physiotherapy compared with conventional intramuscular opiates, and could not distinguish between cryoprobe and intravenous opiate. Roxburgh and co-workers [8] found cryoanalgesia to be no more effective than conventional analgesia in a strict double-blind study. Now we have this confirmed by Müller and associates [2], who found no significant difference between cryoprobe and control groups when looking at pain scores, analgesic consumption, and peak flow rate.

So there are several reports of cryoanalgesia failing to improve postoperative lung function and pain on movement, particularly in the first 48 hours postoperatively. It therefore fails in the most fundamental measure of satisfactory analgesia. If there is no improvement in lung function, how can we expect cryoanalgesia to reduce the incidence of postoperative pulmonary complications? Perhaps the most significant condemnation of cryoanalgesia comes from Dr Katz himself, who tells us that he uses epidural narcotics for the first two postoperative days anyway.

In the penultimate paragraph of his editorial, Dr Katz tries to suggest that the high incidence of postthoracotomy dysesthesia reported by Müller and associates is unusual. We are told that Dr Katz has "heard others talk of this complication," but that as far as he is aware he has only seen one such complication. How can he set this against a well-documented series confirmed by other workers [9]?

We should not be using cryoanalgesia anyway. Dr Katz has failed to reply to the well-presented evidence of other workers in Müller's paper (p 17) who have not found any advantage in using it over conventional opiates. His editorial perpetuates a technique that has been shown to offer no advantage at a time when far more satisfactory methods of pain control are available [10, 11].

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Reply

To the Editor:

In response to the reply by Drs Berrisford and Sabanathan to my editorial on cryoanalgesia, let me take exception to the comment that the editorial [1] was one of just impressions and not facts.

Berrisford and Sabanathan, in condemning the efficacy of cryoanalgesia, base their opinion on the article by Müller and associates [2] and disregard the previous reports because "these studies used small populations" or "failed to use an untreated control group." The facts are that the paper by Müller and associates had a study group of 63 patients divided into the cryoanalgesia group and a control group. Other studies in the literature [3–5] quoted by Berrisford and Sabanathan included more than 600 patients receiving cryoanalgesia therapy. Berrisford and Sabanathan quote Orr and associates [6] as suggesting that cryoanalgesia was not any better in relieving postoperative pain than continuous intravenous morphine administration. To me this indicates a very high degree of efficacy for cryoanalgesia. Our study [5] in which cryoanalgesia, intercostal nerve blocks, and parenteral narcotics were studied in a controlled manner also indicated the superiority of cryoanalgesia. Since the original publication of our study in *Lancet* in 1980 we have used cryoanalgesia for postthoracotomy pain with great success; just ask our surgeons, nurses and patients.

Another point about cryoanalgesia that was not addressed in the original paper nor in my editorial was the prolonged analgesic component that it offers. The need for narcotic medication after the first couple of days postoperatively throughout the weeks and months after operation has been minimal [4].

Concerning the dysesthesias mentioned in the letter by Berrisford and Sabanathan, I would again refer to the statement made in my editorial. It is quite probable that the dysesthesia (and the incidence is extremely low) is indeed secondary to nerve injury done at the time of operation which becomes apparent when the cryoanalgesia wears off. Histological evidence in animal nerves frozen using the same techniques did not indicate the presence of neuromas or neuritis in any of the nerves studied.

In summary, I would like to restate my position on cryoanalgesia. It is an effective means of producing immediate postoperative analgesia that persists for weeks to months after operation. It does not produce total pain relief because the pain after thoracotomy involves not only the incision site but also the disruption of midback structures as well as the irritant effect of the chest tube. When cryoanalgesia is supplemented with other pain-relieving modalities for the first day or two after thoracotomy, the patient has minimal discomfort during the entire postoperative course. I would suggest to Dr Berrisford and Dr Sabanathan that they do not condemn a technique that they probably have not used and that others have adapted as part of their routine on the basis of one paper. When properly done, cryoanalgesia techniques provide an important addition to our armamentarium for pain relief.

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Ectopic Ossification After Median Sternotomy

To the Editor:

My colleagues and I read with interest the article by Vander Salm and associates [1] on ectopic ossification after median sternotomy. In 1980, we published our experience with this entity [2]. In our 2 cases, the patients did well on analgesic therapy. We hypothesized that the ectopic bone may have formed from the wound being seeded by periosteum or perichondrium from the xiphoid process. In previous work by Huggins [3], it was shown that bone will form around bladder mucosa that is transplanted into the rectus sheath of dogs or rabbits. Expanding on Huggins' work, we also hypothesized that rectus sheath metaplasia could be another cause for the ectopic bone formation.

It is interesting to note that the pathophysiology of this entity has still not been fully elucidated over the last 10 years although the theoretical possibilities are pretty much unchanged.

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Empyema Thoracis

To the Editor:

As a thoracic surgeon and as a Frenchman, I feel indebted to Dr Evarts A. Graham for two reasons: first, he wrote in 1933 that surgical resection of a bronchial carcinoma was the only hope for cure and he certainly could repeat himself today with some benefit; but, before that, he saved many lives while working with the Empyema Commission in my country in 1918. To supplement the historical perspective of Dr Richard M. Peters [1], I would like to send you the story of a soldier of the First World War, as was told to me by himself 4 years ago.

> During the last days of July 1918, I was then 19 years old, we attacked Noyon and were hit by gas shells; our masks were soon inefficient. We were evacuated to an infirmary, then to a field hospital. The most severely intoxicated soldiers were brought to Chaumont, ten days after the attack. I was much infected and lost my consciousness. Later on, the Sisters told me what had happened: a rubber tube was put in my pleura and it evacuated a large amount of pus. I improved immediately. Then my temperature rose again. Doctors were worried. I vomited some pus and after that things went better. One week later I was on my feet and they took off the tube through which drugs had been injected. The other soldiers in my ward were operated on with a tube; 15 out of 20 survived. In another wing

> of the hospital, soldiers were operated on with a cut in the chest; almost all of them died.
>
> Two American doctors were working with the French surgeons. One of them was tall, clean-shaven, wearing rimless glasses.
>
> I had a recovery leave in Nice, then went back to the front line in October, as my unit was getting ready for a new attack, but the armistice came.

This short story, from a living witness of Dr Graham's beneficial action at a time when empyema was an important cause of death, is indeed a moving testimony to a young surgeon's remarkable thought and action.

It probably relates one of the first clinical experiences of Dr Graham in France, when open pleurotomy for empyema was still the common—and dangerous—practice. Retrospectively it might be regarded as a dramatic "randomization" between closed and open drainage.

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Reference

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Oxygenator Failure

To the Editor:

We read with interest the recent article by Robblee and associates [1] and the accompanying editorial by Dr E. Converse Peirce II [2]. More recent, albeit retrospective, information is available regarding the incidence of oxygenator failures during cardiopulmonary bypass. In late 1985 our group [3] surveyed clinical perfusionists in the United States and Canada regarding perfusion mishaps. The survey was modeled, in part, on the earlier survey [4] of cardiac surgeons by Stoney and co-workers. More than 600 questionnaires were returned representing 575,000 open heart operations performed in the 3-year period prior to October 1985.

Whereas the study by Stoney and co-workers reported 124 instances of inadequate oxygenation of which only eight resulted in a patient outcome of permanent injury or death, our respondents reported 506 instances resulting in 10 permanent injuries and 32 deaths. (Stoney and associates also reported 16 instances of oxygenators that leaked.) We believe the increased incidence rate of this particular accident can be partially explained by a difference in wording on the two survey questionnaires. Stoney and co-workers asked for the number of accidents related to "failure of oxygen delivery to pump," whereas we asked, "Have you observed life-threatening inadequate oxygenation during cardiopulmonary bypass?" Differences in the target sample group (cardiac surgeons versus clinical perfusionists) also may have accounted for the different responses.

In follow-up questions, we asked what type of oxygenator was in use during the failures and found that 55% of the time it was a bubble type and 45% a membrane oxygenator. More importantly, we asked if an oxygenator had to be changed out during cardiopulmonary bypass. One third of the respondents said that they had done this during 365 cases with the following patient outcomes: 333, no injury; 4, permanent injury; and 23, death (5 outcomes were not reported).

Concerning the case report of Robblee and associates [1], Peirce [2] is probably quite correct in suggesting that oxygenator failures (whether iatrogenic or due to a manufacturing defect) are not unique events. Details of at least eight oxygenator failures were reported by our respondents [5] and included the following mechanisms: (1) a hollow fiber membrane that circumferentially ruptured between the heat exchanger and oxygenation compartment when overpressurized; (2) two bubble oxygenators that had no defoamer agent; (3) 2 cases of leaks in the gas delivery line due to either a hole in a high pressure line or a cracked oxygen line filter; (4) misconnected gas supply lines; (5) failure due to a part missing inside an oxygenator that was not detected before bypass; (6) failure of an oxygen/air blender; and (7) structural failure due to leakage of a volatile anesthetic (Forane) onto the oxygenator (a complication that recently has been reported elsewhere) [6–10].

The thrust of Peirce's editorial [2] is to call for a more widely available reporting mechanism and the development of consensus standards for oxygenators. We concur and would suggest that, at least, the beginnings of a reliable reporting system already exists. The Emergency Care Research Institute (ECRI), with financial support from the American Society of Extra-Corporeal Technology, has recently begun publishing a newsletter called *Technology for Perfusion*. Included in each issue are alerts of reported problems, hazards, and recalls on cardiovascular equipment. These alerts are drawn from the larger ECRI data bases ("Health Devices Alerts") and include information from published literature, Food and Drug Administration (FDA) Enforcement Reports, and recall notices from manufacturers. In addition, the Federal "Medical Device Reporting" mechanism has been in effect since December 1984 and provides for mandatory reporting of device problems that manufacturers become aware of when death or serious injury resulted, or could result, and the device was either the cause or was contributory.

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James F. Arens, MD

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bubble oxygenator. Proc Am Acad Cardiovasc Perfusion 1987;8: 177–81.
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Hypoxemia After Intraluminal Oxygen Line Obstruction During Cardiopulmonary Bypass

To the Editor:

I read with interest the account by Robblee and associates [1] of their experience with occlusion of the oxygen inlet port of the bubbler oxygenator during cardiopulmonary bypass. Although I feel Robblee and associates have brought up some good points, I think they have missed a most important lesson to learn in their near-tragic incident. The use of bubble oxygenators requires that a continuous flow of oxygen (at least 2 L/min) must be maintained at all times including before and after bypass. If there is a sudden discontinuance of gas flow, the hydrostatic pressure of the fluid (ie, blood or crystalloid products) will cause blood or fluid to drown the disperser plate and enter the oxygen line.

I have administered undiluted mannitol in my prime and during bypass without any untoward effects on oxygenation of the blood, because I maintain at least 2 L/min gas flow through the bubble oxygenator at all times.

Timothy A. Dickinson, CCP, MHA

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2075 E Flamingo Rd
Las Vegas, NV 89119

Reference

1. Robblee JA, Crosby E, Keon WJ. Hypoxemia after intraluminal oxygen line obstruction during cardiopulmonary bypass. Ann Thorac Surg 1989;48:575–6.

Reply

To the Editor:

It is interesting that an anecdotal report of an unusual life-threatening complication during the conduct of cardiopulmonary bypass would result in sufficient interest to warrant an editorial and correspondence. However, on reflection, it is appropriate that attention be focused on the larger problem of complications of cardiopulmonary bypass.

Kurusz and colleagues, in their letter, cite a large retrospective study conducted by clinical perfusionists. An earlier study by Stoney and colleagues [1] was conducted by cardiac surgeons. These surveys are both valuable and at the same time misleading. They are valuable because they heighten the awareness that cardiopulmonary bypass is not a benign procedure. They also show that the incidence of problems resulting in poor outcome is not decreasing with time. Although these studies involved large numbers of patients, they were retrospective. We suspect that they understate the extent of the problem.

Dr Peirce, in his editorial, points out that consensus standards for cardiopulmonary bypass circuits do not exist in the United States. Nor do they exist in Canada. We believe that the development of consensus standards for cardiopulmonary bypass circuits is essential before any progress will be made in reducing the incidence of complications. These standards should be developed not only by cardiac surgeons as suggested by Peirce, but also by anesthesiologists and clinical perfusionists.

We also believe that a uniform reporting mechanism should be developed for problems relating to cardiopulmonary bypass circuits. Reporting should include errors in the conduct of cardiopulmonary bypass. This would clearly necessitate multidisciplinary reporting.

Dickinson, in his correspondence, indicates correctly that "a continuous flow of oxygen (at least 2 L/min) must be maintained at all times." This caution, however, does not eliminate the possibility of human error, which may arise particularly in the emergency situation. Nor does it preclude the possibility of disruption of the oxygen gas line as a result of unrecognized disconnection. In our view, the use of checklists similar to those used by anesthesiologists before the induction of anesthesia should be developed by clinical perfusionists under the aegis of cardiac surgeons and anesthesiologists.

We believe that these suggestions, if implemented, could lead to a reduction in the number of life-threatening complications of cardiopulmonary bypass.

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1. Stoney WS, Alford WC Jr, Burrus GR, et al. Air embolism and other accidents using pump oxygenators. Ann Thorac Surg 1980;29:336–40.

Reply

To the Editor:

The good news in the excellent letter of Kurusz, Conti, and Arens is (1) the report of a follow-up to the 1980 survey data published by Stoney and associates on "air embolism and other accidents of perfusion" and (2) the advice that there has been in place, since 1984, a Federal requirement for mandatory reporting by manufacturers of medical device problems that did, or could, result in death or serious injury. Kurusz and colleagues further advise that a data base of medical device problems is maintained by the ECRI, and that the American Society of Extra-Corporeal Technology finances distribution to their members of a newsletter called *Technology for Perfusion*, published by the ECRI and based on pertinent information from this data base.

The bad news starts with the evidence that serious clinical perfusion problems still continue and may increasingly involve the oxygenator. For example, bubble oxygenators may have missing parts or no antifoam; membrane oxygenators may rupture or fail to oxygenate properly. Kurusz and colleagues received information in their survey of 506 instances of inadequate oxygenation (approximately 1/1,000 perfusions). Three hundred sixty-five oxygenators apparently required replacement during cardiopulmonary bypass and at least 23 of the patients being perfused died.

The bad news continues when the subject of data reporting and the dissemination of vital information is further pursued. The two referenced articles based on this 1985 survey were in the *Proceedings of the American Academy of Cardiovascular Perfusion*, an organization of perfusionists, with about 60 active and 250 associate members, that meets yearly. This publication, containing information of vital consequence to the proper care of perfusion patients, is apparently printed in only 850 copies and is distributed to perfusionists, not to cardiac or thoracic surgeons. Articles in it turn out not to be referenced in the Index Medicus and thus not accessible through the popular modem program Grateful.Med. The *Proceedings* is not available in any library in the greater New York City area. My information indicates it is held in libraries only in Texas, Arizona, and Maryland (National Library of Medicine). It was fortunately possible to secure facsimile copies from the National Library of Medicine with only a personal visit to the local Mt. Sinai Library. The survey by Kurusz and colleagues is a valuable document that required nearly a year to prepare. It, or a synopsis, should be high-priority reading for all surgeons who practice, or aspire to perform, heart surgery.

What of the ECRI newsletter? Surely this fills any gap and keeps surgeons informed. This newsletter, one of ten published by ECRI, turns out to have an edition of 3,000 copies, which are distributed principally to members of the American Society of Extra-Corporeal Technology. These, by and large, are perfusionists, not surgeons.

Well and good, perfusionists are certainly advised of oxygenator problems, but what exactly is the status of the ECRI medical device data base? A primary source of information for it is the FDA. It has so far not been possible to determine that the oxygenator failure on which the case report of Robblee and associates was based had been reported to the FDA by Bentley Laboratories. Perhaps this is because the accident occurred in Canada or perhaps this is an example of problems with reporting by users and manufacturers now being addressed by Congress. The September-October 1989 *AAMI News* [1] (the official newsletter of the Association for the Advancement of Medical Instrumentation) reports "Congress is seriously considering legislation that would require hospitals to report directly to the FDA injuries or deaths and certain malfunctions associated with medical device failures . . . reports from the General Accounting Office (GOA), Congress' investigative body, suggest that hospitals have not been reporting mishaps to manufacturers, and that consequently the FDA has not received important information that could significantly enhance its ability to regulate the safety and efficacy of medical devices." Thus the data base also is in question.

The last paragraph of the letter by Kurusz and colleagues correctly reports that the (intended) thrust of my editorial was to call for improved reporting and the (resumption of) development of consensus oxygenator standards. The need for these things is real and their attainment will only come if and when such organizations as the Society of Thoracic Surgeons take official interest and exert leadership to bring them about. Perfusion is certainly not safe!

I was struck by the recent communication from The Society of Thoracic Surgeons [2]. They have formed "an ad hoc committee to study the problem" of practitioners who lack formal training or experience providing perfusion backup for complications of coronary angioplasty. It is stated "all American Board of Thoracic Surgery diplomates are qualified by virtue of education and examination and most are currently experienced in the supervision of [extracorporeal circulation]." Some might think this an inaccurate, and arrogant, statement made in an attempt to regain lost turf.

If the best interest of patients is the objective, thoracic surgeons will become officially involved in improving the clinical perfusion data bases and distributing information better. They will also consider officially the long-term need for American (and international) consensus standards of oxygenators and perfusion systems.

E. Converse Peirce II, MD

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One Gustave L. Levy Place
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The Use of Extracorporeal Circulation (ECC) for Circulatory Support During PTCA

Introduction

The increasing use of extracorporeal circulation (ECC) outside the operating room environment is a trend in which many members of The Society of Thoracic Surgeons have participated. However, its potential for application by practitioners who lack formal training or experience in the technology raises issues of patient safety. Therefore, The Society appointed an ad hoc committee to study the problem and submit a report. The Council of The Society of Thoracic Surgeons endorsed the following statement during the Annual Meeting held in Baltimore in September 1989.

Statement

Extracorporeal circulation was introduced into clinical use by Dr John Gibbon in 1953. Since then, the technology has undergone modification and is applied widely today for surgical treatment of diseases of the heart and great vessels.

The use of ECC traditionally has been under the direct supervision of the thoracic surgeon, the only medical specialist whose formal training and certification require theoretical knowledge and practical experience (case load requirements) with ECC including a thorough understanding of the scientific aspects, necessary apparatus, and complications associated with its use.

The distribution of blood flow during ECC, rheologic effects, impact on various organ systems (lungs, kidneys, immune system, clotting mechanisms), and the effects of hemodilution, hypothermia, and nonpulsatile flow are examples of the knowledge required of thoracic surgeons who are distinguished from other surgical specialists by their routine use of this technology in surgical applications.

Of great concern is the potential for patient injury with ECC. Vascular injury due to cannulation, aortic dissection, air embolism, thrombosis, hemolysis with resultant renal injury, hemorrhage, protamine reactions, and failure to provide adequate perfusion are but a few of the potential hazards of ECC, many of which may be fatal. Less obvious is the cumulative, time-related cellular injury associated with ECC.

In addition to its use in operations on the heart and great vessels, ECC is applied in a limited way for other purposes such as treatment of hypothermia, limb perfusion for melanoma, hypothermia and circulatory arrest for certain neurosurgical procedures and for treatment of renal cell carcinoma with tumor extension into the inferior vena cava and atrium. These applications are undertaken in the operating room under the direct supervision of the thoracic surgeon.

Less commonly, ECC technology may be applied outside the operating room for the other purposes such as extracorporeal membrane oxygenation (ECMO) used in the intensive care unit setting to treat reversible lung injury, or in the critical care unit or cardiac catheterization laboratory for patients in cardiogenic shock.

Medical specialists other than thoracic surgeons may be involved in the applications of ECC. Anesthesiologists who provide anesthesia for cardiac surgery are familiar with the administration of heparin, protamine reversal, and the effects of ECC on cardiopulmonary responses in the anesthetized patient. The vascular surgeon may become involved in treatment of vascular complications of ECC.

The perfusionist is knowledgeable in the physiology of ECC and has proficiency with the pump-oxygenator apparatus.

Supported Angioplasty

Recently, cannulas have been developed and marketed for percutaneous insertion. This has led to the use of ECC by the non-surgeon who may insert cannulas percutaneously and connect them to portable pump-oxygenator systems for the purpose of circulatory support during catheter interventions on the obstructed coronary artery. Experience with so-called "supported angioplasty" has been reported including six abstracts (five recording clinical experience and one animal study) reported at the American College of Cardiology Meeting in Anaheim, California, April 1989.

It is of concern that ECC during "supported angioplasty" may be conducted without the participation and direct supervision of a physician who is both knowledgeable and experienced in the technique. There exist a few non-surgeons who, because of professional commitment and long experience, are so qualified, but these individuals are exceptional. In contrast, all American Board of Thoracic Surgery diplomates are qualified by virtue of education and examination and most are currently experienced in the supervision of ECC. We therefore believe that, except under unusual circumstances, patient safety considerations require formal consultation with the thoracic surgeon whenever use of ECC is contemplated. If ECC is deemed appropriate, then the participation and supervision of a thoracic surgeon or an equally qualified physician is imperative.

We would emphasize the special relationship that exists between the thoracic surgeon and the perfusionist in which the perfusionist functions under the supervision of the thoracic surgeon. In instances in which the perfusionist is employed by the hospital or functions as an independent contractor and is asked to provide perfusion services under a physician not trained in ECC, serious liability questions may be raised for the hospital, perfusionist, physician and manufacturer.

This position paper was also endorsed by the Council of The American Association for Thoracic Surgery in January 1990, and, by prior agreement, is being published in both *The Annals of Thoracic Surgery* and *The Journal of Thoracic and Cardiovascular Surgery*.

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Southern Thoracic Surgical Association Rules for Submission of Abstracts

Abstracts for papers to be presented for the 1990 Annual Meeting are now being accepted. The deadline for postmark of abstracts is May 15, 1990. An original and 1 copy should be submitted, using the official Association abstract form, to Donald C. Watson, Jr, MD, Chairman, Program Committee, The Southern Thoracic Surgical Association, 111 E Wacker Dr, Chicago, IL 60601. Additional forms are available upon request from the Association.

Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. *Abstracts received after the deadline will not be considered.* The information requested at the bottom of this form must be completed indicating who is to receive the notice of acceptance or rejection and who will present the paper if accepted.

Abstracts may be submitted for the regular program, the Forum, or either. Papers selected for the Forum will be published in *The Annals of Thoracic Surgery* if they pass the usual editorial review.

Essayists are reminded that all papers accepted for presentation must be submitted in triplicate to Gordon F. Murray, MD, Secretary-Treasurer, at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation.

Abstracts frequently obscure the value of their content because they are poorly organized. It is important that methods and results be clearly defined in the abstract; general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Presentations in the regular program are limited to 10 minutes; those in the Forum are limited to 5 minutes.

In discussion of papers, the Association encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of the discussion in the form of "secondary papers" will not be welcomed.

INSTRUCTIONS FOR ABSTRACTS

The official abstract form or photocopies must be used. **Authors must indicate whether they want the abstract considered for the regular program, the Forum, or either by checking the appropriate box. Authors must also categorize the principal subject of their abstract by checking the appropriate box.**

1. Title of abstract must be completely CAPITALIZED.
2. Full names of authors must appear on the abstract, without degrees, titles, or appointments.
3. Indicate each author who is a member of the Southern Thoracic Surgical Association with an asterisk following the name.
4. Underline the name of each STSA new member (elected to membership in 1989).
5. Institution or address is to be given.
6. Abstracts must be limited to 200 words and *must be typed double-spaced.*
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    c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
    d. A statement concerning the significance and implications of the work.
9. The form must be signed by the senior author attesting that the material will not be presented elsewhere if accepted for the scientific program nor published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

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I acknowledge that the material will not be presented elsewhere if accepted for presentation on the Southern Thoracic Surgical Association Scientific Program. I further understand that the Editorial Board of *The Annals of Thoracic Surgery* has the right of first refusal for publication of this material.

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Annual Meeting of the International Society for Heart Transplantation, Fort Lauderdale, Florida—April 4–6, 1990

For information on this meeting, contact International Society for Heart Transplantation, 435 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-0828.

Modern Trends in Cardiac and Thoracic Surgery and Reunion of the Mark IV Club, Bristol, England—April 5–6, 1990

The symposium on modern trends in cardiac and thoracic surgery will be followed on April 7 by a reunion of the Mark IV Club (past residents of Ronald Belsey). For information on either of these meetings, contact Mrs Margaret Vickers, Symposium Coordinator, Department of Thoracic Surgery, Frenchay Hospital, Bristol BS16 1LE, England; or telephone 0272 701212, extension 2466.

General Thoracic Surgery, Las Vegas, Nevada—April 19–20, 1990

This meeting is sponsored by the American College of Chest Physicians and the University of Nevada School of Medicine. It is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information on this postgraduate course, contact ACCP, Division of Education, 911 Busse Highway, Park Ridge, IL 60068; or telephone (708) 698-2200.

Thirty-sixth Annual Meeting of the American Society for Artificial Internal Organs, Washington, DC—April 24–27, 1990

For information on this meeting, contact ASAIO Registration, PO Box C, Boca Raton, FL 33429.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870.

Seventieth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada—May 7–9, 1990

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Pulsed Lasers in Angioplasty, Tübingen, Federal Republic of Germany—May 11–12, 1990

This workshop is sponsored by the European Society of Cardiology, the Working Group of Coronary Flow and Angina Pectoris, and the European Association of Radiology. For information on this meeting, contact K. R. Karsch, Department of Cardiology, Medical Clinic, University of Tübingen, Otfried-Müller-Str 10, D-7400 Tübingen, Federal Republic of Germany.

Third International Symposium on Echocardiography and Doppler in Cardiac Surgery, Vienna, Austria—May 9–12, 1990

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450 Vienna, Austria; or telephone +43/1/23 69/2642 (telex: 11 18 03; facsimile: +43/1/23 69/648).

Eleventh Annual Scientific Session of the North American Society of Pacing and Electrophysiology, San Diego, California—May 31–June 2, 1990

For information on this meeting, contact the North American Society of Pacing and Electrophysiology, 13 Eaton Court, Wellesley Hills, MA 02181; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

Eighth Annual Uniformed Services University of Health Sciences Cardiothoracic Surgery Symposium, Washington, DC—May 31–June 2, 1990

For information on this meeting, contact Fred H. Edwards, MD, Department of Thoracic Surgery, Walter Reed Army Medical Center, Washington, DC 20307-5001; or telephone (202) 576-1433.

The Society for Vascular Surgery/International Society for Cardiovascular Surgery, Los Angeles, California—June 4–6, 1990

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Seventh International Congress Cardiostim 90, Nice, France—June 20–23, 1990

Cardiostim gathers several scientific events: Cardiostimulation 90 (cardiac pacing, electrophysiology, defibrillation), International Conference on High-Resolution ECG and Late Potentials, Fifth World Congress on Catheter Ablation, Cardio-Pharmaco 90, and Cardio-Rythmo 90. For information on this meeting, contact Secretariat Cardiostim 90, Department of Cardiac Pacing, Centre Chirurgical Val D'Or, 16, rue Pasteur, 92211 St. Cloud Cedex, France; or telephone (1) 46.02.70.72 (facsimile: (1) 46.02.05.09).

Sixteenth Annual Meeting of The Western Thoracic Surgical Association, Coronado, California—June 20–24, 1990

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Internal Thoracic Artery for Myocardial Revascularization, Toulouse, France—June 27–29, 1990

For information on this meeting, contact the Secretary of the Symposium, Department of Cardiovascular Surgery, Rangueil University Hospital, 31054 Toulouse Cedex, France; or telephone 61.32.26.51 or 61.32.26.53 (telex: 530 826 F).

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

Thirty-ninth Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary—September 9–12, 1990

For information on this meeting, contact Budapest Convention Centre, H-1444, PO Box 233, Budapest XI, Jagello u 1-3, Hungary; or telephone (361) 852-507 (facsimile: (361) 665-636; telex: 22-7717).

Fourth Annual Meeting of the European Association for Cardio-thoracic Surgery, Naples, Italy—September 17–19, 1990

For information on this meeting, contact the Organizing Secretariat, MCM, Rione Sirignano, 5, 80121 Naples, Italy; or telephone (0)81/7611085-7611277 (facsimile: (0)81/664372; telex: 710626).

Interim Meeting of The Society of Thoracic Surgeons, Chicago, Illinois—September 22–23, 1990

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Mechanical Circulatory Support 1990, London, England—September 26–28, 1990

For information on this meeting, contact Anne Sumner, Mechanical Circulatory Support 1990, Medical Research Services, 60 Oxford St, Southampton SO1 1DL, Hants, England; or telephone 0703 231068.

Controversies in Cardiovascular Disease: Surgical Versus Medical Treatment, Aalst, Belgium—September 28–29, 1990

For information on this meeting, contact Dr F. Wellens, Department of Cardiovascular Surgery, O.L. Vrouwziekenhuis, Moorselbaan 164, B-9300 Aalst, Belgium; or telephone 053/78 53 53 (facsimile: 053/78 38 76).

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Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 440 Park Avenue South, New York, NY 10016 (telephone: (212) 684-5540; facsimile: (212) 545-0651). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $15.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3695). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

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Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

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Cardiothoracic surgeon wanted for a busy, expanding, 3-man, private practice group in the Midwest. Applicant must be ABTS eligible or certified. Prefer recent graduate with some background in electrophysiologic surgery. Please send curriculum vitae.

Please respond to Box 189. 189H/G

Cardiovascular and thoracic surgeon wanted to join busy practice in Fort Lauderdale, Florida. Recent US medical graduate preferred.

Please send CV to I. Tabry, MD, 2773 NE 37th Drive, Fort Lauderdale, FL 33308. (Telephone: (305) 561-9781 after 9:00 PM.) 208J/C

Cardiac-thoracic surgeon, needed for expanding program on west coast of Florida. Excellent opportunity, private practice, primarily adult cardiac including cardiac transplantation. BC/BE required. Please send CV.

Please respond to Box 226. 226K/D

Cardiothoracic surgeon, BE/BC, wanted to join surgeon in active cardiac/thoracic/vascular surgical practice in northern Alabama community of 80,000 (300,000 population draw). Clinical practice in two community hospitals. Lake/mountain recreation facilities. Generous compensation, future partnership.

Please write Sara Fleming, Business Manager, 801 Gaines Ave, Suite 305, Gadsden, AL 35903; (205) 492-9360. 237L/E

Associate Director for Heart Transplantation is urgently needed for rapidly expanding heart transplantation program in California.

Please respond with curriculum vitae to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 240L/K

Assistant surgeon—experienced in cardiothoracic surgery to first assist in the operating room. Active adult and pediatric cardiovascular surgery practice in southern California.

Please respond with curriculum vitae and outline of surgical experience to the Pacific Cardiothoracic Surgery Group, 201 S Alvarado St, Suite 626, Los Angeles, CA 90057. 241L/K

Cardiothoracic and vascular surgeon, BC/BE, recent graduate to join private practice of adult cardiac, pulmonary, and vascular surgery located in New Jersey. Please submit curriculum vitae.

Please respond to Box 243. 243L/C

Cardiovascular and thoracic surgeon, board eligible/certified, wanted to join well-established private practice located in Ft. Lauderdale, FL. Send CV.

Please respond to Box 251. 251L/E

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to Box 252. 252L/F

Thoracic-vascular surgeon wanted to join busy practice in Northeast. Board certified or eligible. Interested in practice of vascular and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 254. 254L/F

Cardiothoracic and vascular surgeon wanted to be first assistant. Twenty years experience preferred. Interested in practice of cardiac, vascular, and thoracic surgery. Excellent benefits package. Send curriculum vitae.

Please respond to Box 255. 255L/F

Cardiothoracic surgeon—to join a 2-man private practice in cardiac, thoracic, and vascular surgery in the Great Lakes region. Must be board certified or eligible. Recent graduates considered. Send curriculum vitae.

Please respond to Box 260. 260L/E

Cardiothoracic surgeon, experienced in cardiac arrhythmia surgery, to join well-established cardiac surgical group in central Florida. Send CV.

Please respond to Box 267. 267A/C

Cardiovascular and thoracic surgeon, BE/BC, to join established private practice in San Francisco Bay area. Practice includes adult cardiac, thoracic, and vascular surgery. Initial contact should include curriculum vitae and references.

Please respond to Box 268. 268A/C

Cardiovascular/thoracic surgeon to complete 3-man group in adult cardiothoracic private practice in Michigan. Must be board eligible or certified. References required.

Please respond to Box 269. 269A/F

Chairperson, Department of Thoracic-Cardiovascular Surgery. Winthrop-University Hospital, a 533-bed tertiary care hospital of SUNY Stony Brook, is seeking candidates to chair its cardio-thoracic department. Applicants should have strong clinical, teaching, and administrative skills, as well as a commitment to research. The department conducts a fully approved open heart program and performs a large volume of thoracic and vascular surgery. The hospital will support a fellowship program and research activities.

Send CV to Alan Fein, MD, Chairman, TCV Search Committee, Winthrop-University Hospital, c/o 222 Station Plaza No., Suite 400, Mineola, NY 11501. 273A/C

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland OR 97213-2282. 274A/F

Cardiovascular and thoracic surgeon: Position available for a board certified or board eligible to join practice in Northeast involved in adult cardiac, thoracic, and vascular surgery. Association will lead to partnership. Excellent fringe benefits. Please send curriculum vitae.

Please respond to Box 275. 275A/F

Cardiothoracic transplant surgeon, board certified or eligible, wanted to join established practice. Experience required in transplantation, adult cardiac surgery, and thoracic surgery. Northwest city with easy lifestyle and outdoor activities. Salary leading to partnership.

Please respond to Box 276. 276A/C

Cardiac surgeon, board eligible/certified, with at least 2 years experience in adult cardiac surgery, wanted to join well-established 2-surgeon practice located in south Florida.

Please respond to Box 277. 277A/C

Cardiac surgeon sought for beautiful Rocky Mountain region. 200 cases per year in a 282-bed regional hospital. Excellent salary and benefits with bonus incentives leading to partnership after third year. Outdoor activities abound in excellent living environment. BC/BE required. Please respond with curriculum vitae and references.

Please respond to Box 280. 280BC

Thoracic surgeon: Excellent opportunity for experienced thoracic surgeon to join well-established hospital-based practice in general thoracic and vascular surgery. Hospital located in attractive New England coastal community and is affiliated with prestigious teaching institutions and medical schools.

Please contact Jeanne Dowrick, Fulton, Longshore & Assocs, 527 Plymouth Rd, Plymouth Meeting, PA 19462; telephone (800) 346-8397 or (215) 834-6780. 284B/D

Cardiovascular and thoracic surgeon, BC/BE, recently trained to join an established 3-man private practice group in Southeastern coastal capital city and two-university town. Great hunting, fishing, and sports. Submit CV and references.

Please respond to Box 293. 293B/E

A busy cardiothoracic group in the NYC area is looking primarily for a thoracic surgeon with potential for cardiac surgery in the future. Excellent salary and benefits. Respond with curriculum vitae.

Please respond to Box 211. 211J/D

Thoracic cardiovascular surgeon to join group of 12 surgeons located in the South. Group also includes physician assistants, perfusionists, perfusion assistants, surgical technicians, registered nurses, and ancillary office personnel. Group philosophy is to practice quality medicine with utmost concern for patient.

Please respond to Box 294. 294C

Cardiothoracic/vascular surgeon, board eligible/certified, wanted to join established group practice in Southeast. Please send curriculum vitae.

Please respond to Box 295. 295C/E

Cardiovascular and thoracic surgeon, BE/BC, to join another physician in a rapidly expanding private practice located in the Southeast. Send curriculum vitae and references.

Please respond to Box 296. 296C/E

Cardiovascular and thoracic surgeon wanted to join private practice in mid-Atlantic state. Please respond with CV.

Please respond to Box 298. 298C/D

Cardiothoracic surgeon, BC/BE, wanted to join well-established, 2-man practice in greater Boston area. Excellent opportunity and benefits.

Please respond with CV to Associated Cardiothoracic Surgeons, Inc, 1180 Beacon St, Brookline, MA 02146. 300C

Thoracic/vascular surgeon to join small group private practice in medium-sized New England community. BC/BE in thoracic surgery. Prefer C/E for Cert. Special Competence in Vascular Surgery. Recent medical graduate preferred. University-affiliated hospital. Full partnership in 3 years.

Please respond to Box 301. 301C/F

Cardiothoracic/vascular surgeon wanted to join established practice in Ohio. Recent graduate preferred. Please submit curriculum vitae and three references.

Please respond to Box 302. 302C/F

Thoracic, vascular, and general surgeon to join a busy, all boarded, private practice on eastern Long Island. Should be board certified or eligible. Excellent salary and benefits, leading to a full partnership. Send curriculum vitae.

Please respond to Box 303. 303C/E

Thoracic and vascular surgeon, board certified, to join active (noncardiac) thoracic and vascular practice in northern New Jersey. Competitive salary and benefits. Please respond with curriculum vitae.

Please respond to Box 304. 304C/E

Cardiovascular/thoracic surgeon, BC/BE, to join established private practice. Desirable location on Florida west coast. Expertise in adult cardiac, vascular, and thoracic surgery required. Recent graduate, transplant experience preferred. Please include curriculum vitae and references with response.

Please respond to Box 305. 305C/D

Chief, General Thoracic Surgery: The University of Pittsburgh School of Medicine Department of Surgery is seeking a general thoracic surgeon. This person will serve as Director of the Section of General Thoracic Surgery within the Division of Cardiothoracic Surgery. Candidates must have board certification or equivalent. Academic rank and salary will be commensurate with experience.

CVs should be forwarded to Richard L. Simmons, MD, Chair, Department of Surgery, University of Pittsburgh, 497 Scaife Hall, Pittsburgh, PA 15261. The University of Pittsburgh is an equal opportunity/affirmative action employer. 306C

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join established 2-man group in Georgia. Good salary leading to partnership. Please send curriculum vitae.

Please respond to Box 307. 307C

Thoracic surgeon. A 230-physician multispecialty prepaid group in Hawaii is seeking a qualified MD to accept the second thoracic surgery position. Must be experienced in adult cardiac, general thoracic, and peripheral vascular surgery. Excellent fringe benefits. Malpractice paid.

Please direct curriculum vitae to Hawaii Permanente Medical Group, Inc, 3288 Moanalua Rd, Honolulu, HI 96819. An equal opportunity employer. 250L/C

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, 45, ABS, ABTS, seeks relocation. Twelve years private practice and university experience.

Please respond to Box 271. 271A/C

42-year-old cardiac surgeon, American trained, ABS certified, ABTS eligible. Currently practicing in the Middle East. Has considerable experience in valve surgery. Wishes to relocate to the US but will require a visa. Would consider joining a group or research project.

Please respond to Box 285. 285B/D

Cardiovascular and thoracic surgeon, American, University trained, 36, wishes to relocate. ABS certified, ABTS eligible. Interested in joining a group or initiating a new program.

Please respond to Box 288. 288B/D

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 222K/D

Fellowship in pediatric cardiovascular surgery available July 1990. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40's.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453; or telephone (312) 857-3029. 253L/D

Postresidency clinical fellowship available in cardiopulmonary surgery with group performing over 1,000 cardiac procedures per year. Up to 25% research opportunity option available. Complete training in cardiopulmonary surgery required. US graduates must be eligible for Oregon license. Foreign medical graduates must be eligible for J-l or H-l visa. Fellowship for 1 to 2 years beginning July 1990 or January 1991.

Please send CV to Albert Starr, MD, 9155 SW Barnes Rd #240, Portland, OR 97225. 287B/D

Fellowship in cardiac surgery available July 1, 1990, at the University of Massachusetts Medical Center.

Send inquiries to John M. Moran, MD, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655. 297C

Fellowship in cardiac surgery available August 1989 at University Hospital Gasthuisberg, Leuven, Belgium. Clinical training in acquired and congenital heart disease (1,300 open heart procedures yearly) as well as research opportunity with generous stipend and benefits. The period of time should not be less than 12 months. The applicant should be advanced in his or her clinical training for at least 3 years. The application must be accompanied by a curriculum vitae and a detailed letter of recommendation from the candidate's department head. The final appointment of the candidate will be made after a personal interview.

Please respond to Prof Dr J. Peers, Medical Director, University Hospitals of the Catholic University of Leuven, Herestraat 49, B-3000 Leuven, Belgium. 299C

Fellowship—Adult Cardiac Surgery—One-year fellowship available at Beth Israel Hospital/Harvard. Excellent salary and benefits. Large volume of surgery and clinical experience under graded supervision. Opportunities for clinical research. Ideal for (BE) CT resident desiring more experience while awaiting staff position, or for general surgical resident (BE) awaiting CT residency.

Please contact Ronald M. Weintraub, MD, 330 Brookline Ave, Boston, MA 02215. Telephone: (617) 735-4323. 308C

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CARDIOVASCULAR

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Excellent benefit package. Affiliated with Texas A&M University College of Medicine.

For details, contact: F. L. Korompai, M.D., Scott & White Clinic, 2401 South 31st Street, Temple, Texas, 76508, 817-774-4910.

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2 positions open for physicians assistants with 6 man Cardiothoracic surgery group. Large volume cardiac and thoracic surgery program. Excellent salary. Please contact:

Dr. Thomas Z. Lajos
Buffalo Heart Surgical Associates
56 Linwood Ave.
Buffalo, NY 14209
Tel. (716) 845-2249

CARDIAC SURGERY FELLOWSHIPS & ASSOCIATE POSITIONS IN CARDIAC SURGERY

The Cleveland Clinic Foundation's Department of Cardiovascular Surgery performs 3000 open heart operations annually with an increasing proportion of either complex procedures or reoperation. Active sections exist in all facets of adult cardiac surgery including: reparative valvular procedures, electrophysiological surgery, cardiac transplantation, and circulatory support. Both clinical and experimental research opportunities exist.

FELLOWSHIP
A 1-2 year fellowship is available for individuals interested in board equivalent training in cardiac surgery. This program covers all aspects of adult cardiac surgery including intensive care unit experience.

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Individuals who have completed their training in Cardiac Surgery who are interested in an additional 1-2 year period of experience in adult cardiac surgery are eligible for the Clinical Associate Position.

Both positions are associated with competitive salaries, opportunities for attendance at national meetings and allotted vacation times. For information please contact: Robert W. Stewart, M.D.

The Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
Cleveland, OH 44195-5066

or call: (216) 444-6708

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Edmonton

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Department of Surgery

Cardiovascular research scientists are invited to apply for the position of Director of laboratory-based Cardiovascular Surgical Research in the Department of Surgery, Faculty of Medicine at the University of Alberta. A stimulating environment and outstanding facility is available for the right individual, preferably with training in CVT Surgery and Ph.D. or M.Sc., computer skills and a proven research record. Minimum salary is $50,000.00 per annum and up with excellent benefits; salary negotiable based on qualifications and experience.

In accordance with Canadian Immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada.

Applicants should send curriculum vitae and the names of three references by April 30, 1990 to:

Dennis L. Modry, M.D., FRCS(C)
Director, Division of Cardiovascular and Thoracic Surgery
2D1.02, WC Mackenzie Health Sciences Centre
Edmonton, Alberta, Canada T6G 2B7

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For further information about this exceptional private practice opportunity, please send a CV to:

Ms. Donna Bowden
East Michigan Cardiovascular Surgery, P.C.
100 Harrow Lane
Saginaw, MI 48603

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The Medical Staff and Administration of Conemaugh Valley Memorial Hospital, a 405-bed major teaching, University-affiliated, regional medical center with level I trauma and helicopter services, seek a leading cardiovascular surgeon to develop a premier open-heart program at our institution. The successful candidate must lend instantaneous credibility to this new program through current recognition as an outstanding clinician. New facilities, an active invasive interventional cardiology program and a free hand in program development await the Director. Clinical and financial success are essentially guaranteed. For additional information regarding this outstanding opportunity in our forward-looking institution and extremely livable community, please contact: **T. Michael White, M.D., Chairman, Department of Internal Medicine, 814-533-9403.**

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1086 Franklin Street Johnstown, PA 15905-4398

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Director, The Jersey Shore Heart Institute

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Senior Lecturer	S$15,000
Associate Professor	S$21,000

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Leave and medical benefits will be provided. Depending on the type of contract offered, other benefits may include: provident fund benefits or an end-of-contract gratuity, a settling-in allowance of S$1,000 or S$2,000, subsidised housing at nominal rentals ranging from S$100 to S$216 p.m., education allowance for up to three children subject to a maximum of S$10,000 per annum per child, passage assistance and baggage allowance for the transportation of personal effects to Singapore.

Application forms and further information on terms and conditions of service may be obtained from:

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Personnel Department
National University of Singapore
10 Kent Ridge Crescent
Singapore 0511

The Director
North America Office
National University of Singapore
55 East 59th Street
New York, N.Y. 10022, U.S.A.
Tel: (212) 751-0331

Enquiries may also be sent through BITNET to: PERSDEPT @ NUSVM, or through Telefax: (65) 7783948

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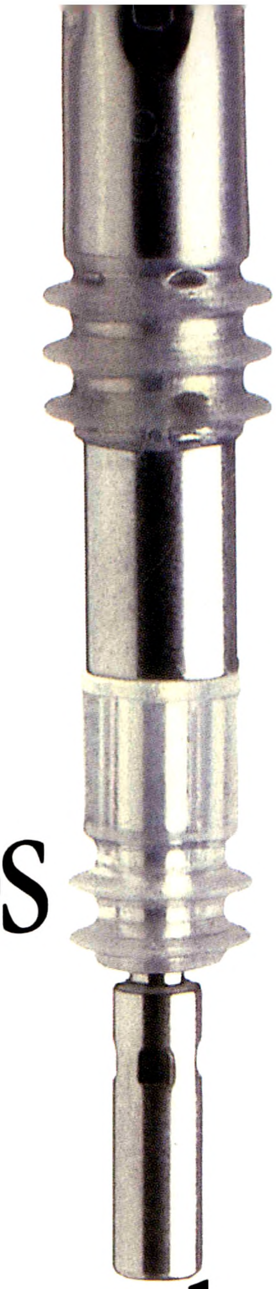

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Please see adjacent page for references and disclosure.

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References

1. Heinemann F, et al: Clinical comparison of available 'low threshold' leads. European Society of Cardiology, Congress, Vienna, 1988.
2. Steinhaus DM, Foley LM: Atrial sensing: A continuing problem? (abstract) *PACE* 1988;11(4):533.
3. IS-1 is the designation of the standard pacing connector developed by the International Committee on Cardiovascular Implants for Surgery (International Standard Organization ISO TC150/SC).

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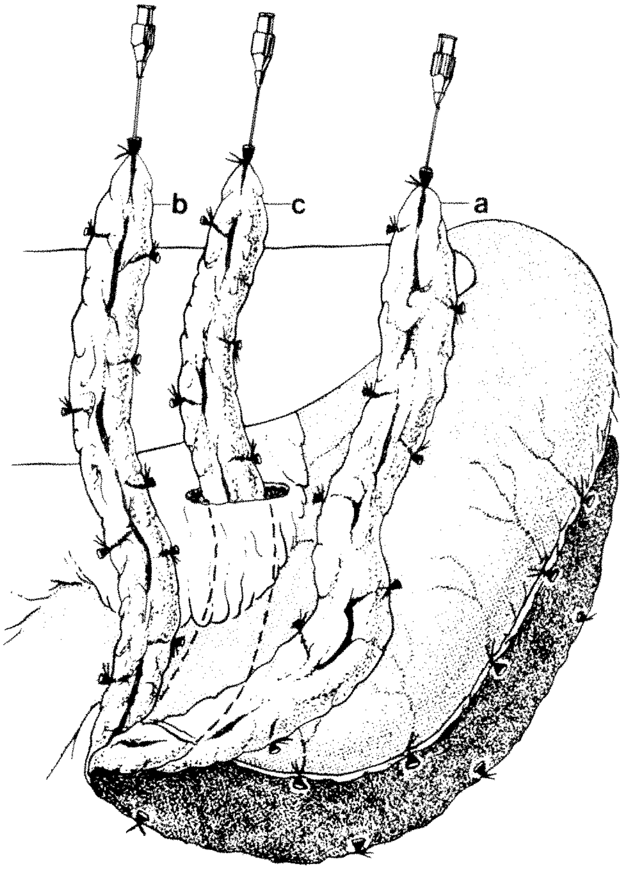

Figure 4. *Routes of the right gastroepiploic graft to the diaphragm are:* **(A)** *anterior to the stomach (rare),* **(B)** *anterior to the duodenum, and* **(C)** *posterior to the stomach through the avascular space in the lesser sac (most common).*

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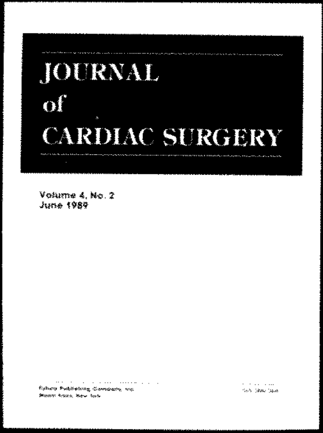

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